FDAMA Section 113:
Status Report on Implementation

Department of Health and Human Services
Food and Drug Administration
Office of Special Health Issues

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TABLE OF CONTENTS

EXECUTIVE SUMMARY

BACKGROUND

Section 113 of the Food and Drug Administration Modernization Act (FDAMA) (42 U.S.C. § 282(j)), enacted November 21, 1997, creates a public resource for information on studies of drugs, including biological drug products, to treat serious or life-threatening diseases and conditions conducted under the Food and Drug Administration's (FDA) investigational new drug (IND) regulations at Title 21, Code of Federal Regulations Part 312. (21 CFR 312). It directs the Secretary of Health and Human Services (HHS), acting through the Director of the National Institutes of Health (NIH), to establish, maintain, and operate a data bank of information on certain clinical trials.

Specifically, Section 113 of FDAMA requires that the Clinical Trials Data Bank contain:

> (1) information about both federally- and privately-funded clinical trials for experimental treatments (drug and biological products) for patients with serious or life-threatening diseases and conditions;
>
> (2) a description of the purpose of each experimental drug;
>
> (3) patient eligibility criteria;
>
> (4) a description of the location of clinical trial sites; and
>
> (5) a point of contact for patients wanting to enroll in the trial.

Section 113 of FDAMA requires that information be forwarded to the data bank by the sponsor of the trial not later than 21 days after the approval of the protocol.[1] It also requires information provided through the Clinical Trials Data Bank be in a form that can be readily understood by the public [42 U.S.C. 282(j)(3)(A)].

The NIH, through its National Library of Medicine (NLM) and with input from the FDA and others, developed the Clinical Trials Data Bank. The first version of the Clinical Trials Data Bank was made available to the public on February 29, 2000, via the Internet at www.clinicaltrials.gov. At that time, the data bank, referred to as ClinicalTrials.gov, contained more than 4,000 records, representing primarily trials sponsored by the NIH. Today, ClinicalTrials.gov includes more than 13,500 federally- and privately- sponsored trials.

[1] *Final Guidance for Industry: Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions* http://www.fda.gov/OHRMS/DOCKETS/98fr/00d-1033_gdl0003.pdf. Because the Agency does not approve protocols, we have interpreted this to mean within 21 days after the trial is open for enrollment.

FDA issued a final guidance to industry on March 18, 2002 to address statutory and procedural issues related to Section 113 of FDAMA. The guidance states that a trial is required to be in the data bank if it is intended to treat a serious or life-threatening disease or condition and is a phase 2, 3 or 4 trial with efficacy endpoints. On January 27, 2004, FDA issued a draft guidance revising the March 2002 guidance to include guidance for sponsors who would be submitting information required by the Best Pharmaceuticals for Children Act. The January 2004 draft guidance is available at http://www.fda.gov/cder/guidance/3901dft.pdf.

In January 2002, FDA's Office of Special Health Issues (OSHI) undertook a multi-faceted project to educate IND sponsors about Section 113 of FDAMA and to assess sponsor compliance with the law. The following section describes the various components of the project.

FINDINGS

The key components of the project are as follows:

- The **Education Program**, initiated in 2002, consisted of mailing letters to IND sponsors of products regulated in the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) that served to inform each sponsor about the requirements of FDAMA Section 113, the availability of the final guidance to industry, and the Protocol Registration System (PRS) available through the data bank. In CDER, 1,748 letters were mailed to sponsors of commercial INDs; 612 were mailed to sponsors of commercial INDs in CBER.

- **Compliance Evaluation Program I** attempted to determine the extent to which sponsors' submissions to CDER were also included in ClinicalTrials.gov. It compared the number of protocols submitted to CDER and to ClinicalTrials.gov for a period of nine months. Of the 2,062 protocols submitted to CDER from January 1, 2002 to September 30, 2002, 688 protocols (33%) were trials to test effectiveness for serious or life-threatening diseases and conditions and met the criteria for inclusion in ClinicalTrials.gov. During that same time period, 239 (35%) of these 688 trials were listed by sponsors in ClinicalTrials.gov.

- In 2004, the project was expanded to include **Compliance Evaluation Program II**, intended to reflect any changes that may have resulted from increased public attention to making clinical trial information more publicly available. For this project, OSHI conducted a review of new cancer protocols submitted to CDER's Division of Oncology Drug Products (n = 140) for a period of three months in 2004. Overall, compliance in listing cancer trials in ClinicalTrials.gov increased from 61% in 2002 to 76% in 2004.

- FDAMA 113 provided for the voluntary inclusion of information about results of clinical trials. ClinicalTrials.gov includes data fields for sponsors to include publication citations or links to educational, research, government, and other non-profit Web pages. In 2004, we reviewed the publication citations about results and whether they were available as no-cost, full text articles. We also reviewed the links sponsors listed in ClinicalTrials.gov. Of the 358 references reviewed, 125 (35%) described human drug studies and 177 (49%) were

available as full-text articles. Of the full-text articles, half were available at no cost. OSHI determined that approximately 51% of the 139 links listed by sponsors were to sponsors' websites. We did not review completed studies to identify published articles reporting the results of the clinical trial.

RECOMMENDATIONS

The Department of Health and Human Services (DHHS) developed ClinicalTrials.gov in response to legislation calling for a publicly-accessible registry of clinical trials for serious or life-threatening diseases and conditions. The response to the legislation has been mixed. Participation by the pharmaceutical industry is lower than expected despite a federal law, a final guidance document, a targeted education program, and an easy-to-use web-based data entry tool. Some pharmaceutical companies list clinical trials but provide limited information, some do not provide information on trials that fall within FDAMA 113, and others voluntarily list trials that go beyond the criteria specified in the statute.

There has been progress on implementing the legislation, however more needs to be done by FDA, pharmaceutical companies, and others to assure increased participation in ClinicalTrials.gov.

- FDA should continue to further clarify messages about which trials and what information should be listed in ClinicalTrials.gov. In November 2004, FDA updated IND acknowledgement letter templates to include a new paragraph reminding sponsors of their responsibility to comply with Section 113 of FDAMA and encouraging the listing of all trials. The draft Guidance for Industry *Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions* will be updated to reflect the findings from our study.

- Pharmaceutical companies and other private sector sponsors are encouraged to review their systems for identifying and submitting protocols to ClinicalTrials.gov. We expect that the number of industry-sponsored trials submitted to ClinicalTrials.gov over the next six months will continue to rise as a result of a recent PhRMA initiative. Under a new voluntary disclosure policy announced in January 2005, PhRMA member companies have agreed to provide information about ongoing hypothesis-testing trials for *all* diseases to ClinicalTrials.gov by September 13, 2005. The policy also encourages PhRMA member companies to establish and make public procedures for verifying compliance with the policy. In addition, the International Committee of Medical Journal Editors (ICMJE) announced their position that new trials must be registered in order to be eligible for publication.[2] Their policy applies to trials that start recruiting on or after July 1, 2005. Ongoing trials are required to be registered by September 13, 2005.

- Patient advocacy groups should continue to be proactive in encouraging FDA and pharmaceutical companies to make information about ongoing trials more available through

[2] September 2004 ICMJE announces clinical trials must be listed in a public trials registry to be considered for publication http://www.icmje.org/clin_trial.pdf and May 2005 http://www.icmje.org/clin_trialup.htm.

ClinicalTrials.gov. Advocacy group initiatives like the Kidney Cancer Association's policy to not list a clinical trial on its website unless the trial is listed in ClinicalTrials.gov are commendable.

FDA will continue to work with sponsors to encourage their entry of required and voluntary information into ClinicalTrials.gov. We believe that a comprehensive clinical trials database can lead to more efficient and timely answers to scientific questions that will result in earlier access to effective treatments for patients.

INTRODUCTION

Time is a precious commodity for many patients who run out of standard treatment options and want to explore participation in a clinical trial. Learning what trials are being conducted, where they are taking place, and who is eligible to participate can be a challenge, especially if a patient has a serious or life-threatening disease.

At the same time, recruiting patients to clinical trials is time consuming and costly for the pharmaceutical industry. Everyone - clinical trial sponsors, patients, and patient advocates - has an interest in facilitating the studies to evaluate new treatments for serious illnesses.

In 1997, the U.S. Congress addressed the needs of patients and their advocates by adding a provision to the Food and Drug Administration Modernization Act (FDAMA) that mandated the establishment by the National Institutes of Health (NIH) of a publicly-accessible clinical trials data bank and required sponsors to list eligible trials in the data bank. The NIH, through its National Library of Medicine (NLM), developed the Clinical Trials Data Bank called ClinicalTrials.gov. This service was made available to the public in February 2000 at www.clinicaltrials.gov.

In January 2002, the Food and Drug Administration (FDA) Office of Special Health Issues (OSHI) undertook a study to investigate listings of study protocols in the Clinical Trials Data Bank. The effort resulted in multiple projects on various issues related to the topic.

The first two projects were intended to educate private-sector sponsors about the statutory reporting requirements under Section 113 of FDAMA and to assess sponsor compliance with the law. The results of these projects stimulated questions about whether the number of clinical trial listings submitted by sponsors to the clinical trials data bank was increasing over time. Consequently, in May 2004 another project was initiated to further assess compliance and, if possible, identify sponsors' reasons for not complying. Recent attention to publicly available clinical trial results prompted another project that reviewed what additional information sponsors were voluntarily including in their submissions to the data bank. This report will examine each of these issues.

HOW THIS REPORT IS ORGANIZED

This report describes our key findings and is structured as follows:

- **Chapter 1: Background** explains the history of the Clinical Trials Data Bank and the FDA guidance documents implementing the requirements of the data bank.

- **Chapter 2: Education Program** describes the objectives, methods, and results of the project intended to educate private-sector investigational new drug (IND) sponsors about the statutory requirements, FDA guidance documents, and web-based entry tool for the Clinical Trials Data Bank.

- **Chapter 3: Compliance Evaluation Program I** describes objectives, methods, and results for the part of the project in which we examined the extent to which trials submitted to the Center for Drug Evaluation and Research (CDER) that were required to be submitted to the Clinical Trials Data Bank were actually submitted to the data bank.

- **Chapter 4: Compliance Evaluation Program II** describes the objectives, methods, and results for the project that investigated whether there has been an increase in the number of cancer trials submitted to the Clinical Trials Data Bank. In this section, we also discuss some additional reasons why we believe sponsors may not have listed trials on the data bank.

- **Chapter 5: Public Availability of Information** explores the degree to which information not submitted to the Clinical Trials Data Bank was found on other publicly available resources.

- **Chapter 6: Reporting Clinical Trials Results** discusses the objectives, methods, and results for the project that investigated what additional information with respect to clinical trial results sponsors were voluntarily submitting to the Clinical Trials Data Bank.

- **Chapter 7: Limitations** discusses the limitations of the various projects.

- **Chapter 8: Summary** provides the current status of implementation for FDAMA Section 113 and suggests some considerations for the future.

- **Glossary:** See Appendix A for a list of key acronyms and definitions contained in the report.

CHAPTER 1. BACKGROUND

I. ClinicalTrials.gov - the Clinical Trials Data Bank

Section 113 of FDAMA (42 U.S.C. § 282(j)), enacted November 21, 1997, creates a public resource for information on studies of drugs, including biological drug products, to treat serious or life-threatening diseases and conditions, conducted under the FDA's IND regulations at Title 21, Code of Federal Regulations Part 312 (21 CFR 312). It directs the Secretary of Health and Human Services (HHS), acting through the Director of the NIH, to establish, maintain, and operate a data bank of information on clinical trials.

Specifically, Section 113 of FDAMA requires that the Clinical Trials Data Bank contain:

> (1) information about both federally- and privately-funded clinical trials for experimental treatments (drug and biological products) for patients with serious or life-threatening diseases and conditions;
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[3] *Final Guidance for Industry: Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions* http://www.fda.gov/OHRMS/DOCKETS/98fr/00d-1033_gdl0003.pdf Because the Agency does not approve protocols, we have interpreted this to mean within 21 days after the trial is open for enrollment.

II. Guidance Documents

FDA issued two draft guidances, a final guidance, and another draft guidance to address statutory and procedural issues related to Section 113 of FDAMA. Details of these guidance documents are described below.

March 29, 2000 *Federal Register* (65 FR 16620)
Draft Guidance for Industry: Information Program on Clinical Trials for Serious or Life-Threatening Diseases: Establishment of a Data Bank.[4]

- Provided the pharmaceutical industry and other IND sponsors with recommendations on submitting trial information to the Clinical Trials Data Bank.

- Included information about the types of clinical trials for which submissions to the Clinical Trials Data Bank are required under FDAMA Section 113 as well as the content of those submissions.

July 9, 2001 *Federal Register* (66 FR 35798)
Draft Guidance for Industry: Information Program on Clinical Trials for Serious or Life-Threatening Diseases: Implementation Plan.[5]

- Addressed procedural issues, including how to submit required and voluntary trial information to the Clinical Trials Data Bank, and requests for an exemption to list a trial.

- Proposed a time frame for submitting the information.

March 18, 2002 *Federal Register* (67 FR 12022)
Final Guidance for Industry: Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions.[6]

- Combined the two draft guidances into a single document and incorporated comments received on the draft guidances.

January 27, 2004 *Federal Register* (69 FR 3923)
Draft Guidance for Industry: Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions.[7]

- Revised the March 2002 guidance to include guidance for sponsors who will be submitting information required by the Best Pharmaceuticals for Children Act (BPCA).

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[4] See http://www.fda.gov/OHRMS/DOCKETS/98fr/001033gl.pdf
[5] See http://www.fda.gov/OHRMS/DOCKETS/98fr/001033gd.pdf
[6] See http://www.fda.gov/OHRMS/DOCKETS/98fr/00d-1033_gdl0003.pdf
[7] See http://www.fda.gov/OHRMS/DOCKETS/98fr/2004d-0014-gdl0001.pdf

- The new information required by the BPCA includes a description of whether, and through what procedure, the sponsor of the research will respond to requests for access to the therapy outside of the clinical trial setting, particularly in children.

CHAPTER 2. EDUCATION PROGRAM

This chapter describes the project intended to educate private-sector IND sponsors about the Clinical Trials Data Bank.

I. Objectives

The objectives of the **Education Program** were to inform private-sector IND sponsors about the following:

1. Statutory requirements for the Clinical Trials Data Bank under FDAMA Section 113

2. The 2002 guidance *Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions*

3. The availability of the Protocol Registration System (PRS), a web-based data entry tool

II. Methods

The education program consisted of mailing letters to IND sponsors of products regulated in CDER and the Center for Biologics Evaluation and Research (CBER) that served to inform each sponsor about FDAMA Section 113 requirements, the availability of the final guidance to industry, and the PRS.

Due to resource limitations, we only sent letters to "commercial" IND sponsors.[8] We did not send letters to NIH, even for protocols classified as commercial, because the NIH institutes were already listing trials in ClinicalTrials.gov using procedures that had been developed prior to issuance of FDA's guidances.

A. CDER

A letter was mailed to the sponsor each time it submitted a new commercial protocol to a CDER IND (see appendix B for a copy of the CDER letter). Letters were created on a weekly basis throughout the duration of Compliance Evaluation Program I, from February through November 2002.

For a more detailed description of the process used to prepare the CDER letters, see appendix C.

[8] http://www.fda.gov/cder/guidance/3082fnl.pdf When FDA receives an IND it is categorized as either "commercial" or "research." A commercial IND is one in which the sponsor is a corporate entity (rarely, some other organization seeking to develop a drug for marketing); a research IND sponsor is typically an individual investigator, academic institution, or the NIH. FDA may designate an IND as commercial if it is clear the sponsor intends the product to be distributed in interstate commerce at a later date.

B. CBER

Due to resource limitations, we did not obtain individual CBER protocols on an on-going basis. Rather, we obtained a list identifying each active CBER IND. Active INDs were grouped by sponsor and company contact person. Each company contact person was sent the same letter that CDER sponsors received but instead of referencing a specific protocol, it contained a list of that sponsor's active INDs (see appendix D for a copy of the CBER letter).

For a more detailed description of the process used to prepare the CBER letters, see appendix E.

II. Results

For CDER INDs, **1748 letters** were mailed to **sponsors of 1012 commercial INDs** over the ten-month period of February to November 2002.

For CBER INDs, **612 letters** were mailed to **sponsors of 1388 commercial INDs** during May 2002.

III. Discussion

We did not request a formal response from each sponsor. On occasion we received written correspondence from a sponsor acknowledging the letter and stating the sponsor would review the referenced protocol to determine whether it met the listing criteria. If the protocol met the listing criteria, the sponsor would list the trial in ClinicalTrials.gov.

Throughout the duration of the education program, we evaluated what proportion of protocols submitted to FDA that were required to be submitted to ClinicalTrials.gov had actually been submitted for inclusion. This evaluation will be further explored in the next chapter.

CHAPTER 3. COMPLIANCE EVALUATION PROGRAM I

This project attempted to determine the extent to which sponsors' IND submissions to CDER were included in the Clinical Trials Data Bank. It compared the number of trials submitted to CDER and to ClinicalTrials.gov for a period of nine months. CBER protocols were not evaluated for this project.

I. Objective

The objective of Compliance Evaluation Program I was to assess regulatory compliance with Section 113 of FDAMA by comparing the number of trials listed in ClinicalTrials.gov to the number of commercial protocols submitted to CDER between January 1, 2002 and September 30, 2002.

II. Methods

Data for the first evaluation program were obtained from two primary sources within the agency: Center ORACLE Management Information System (COMIS), and paper protocol records submitted by IND sponsors. New commercial protocols submitted to CDER between January 1 and September 30, 2002 were identified from a search of the COMIS database. The COMIS search included both new protocols and new INDs because it was assumed each new IND submitted contained at least one protocol.

A. Data collection

Each week we received an electronic file containing each new commercial protocol submitted to CDER the previous week. The file was downloaded into a Microsoft Access™ database we developed for the project, hereafter referred to as the OSHI database. Each week the CDER document room staff delivered copies of the paper INDs. By project's end, a total of 1,865 paper INDs were delivered to OSHI.

For a complete description of the data collection process see appendix F.

B. Data extraction

The following key data elements were extracted from 2,062 protocols and entered into the OSHI database using the Protocol Form 2 (see appendix G for a copy of Form 2):

- Indication: The indication provided by COMIS was revised using NLM's controlled vocabulary thesaurus known as Medical Subject Headings (MeSH) (http://www.nlm.nih.gov/mesh/MBrowser.html). MeSH was used to provide consistency in the indication data field and enabled us to accurately and efficiently calculate the number of protocols per disease.

- Sponsor type: Industry (pharmaceutical company), NIH, Other Government, Physician, Medical Center, Other

- Protocol number: Sponsor designated protocol identifier

- Protocol title: Title of protocol

- Number of protocols within the submission

- Phase: 1, 1/2, 2, 2/3, 3, 3/4, 4, Not Specified (NS)

  If the phase was not mentioned in the title or protocol synopsis then the phase listed on FDA Form 1571 was used. We used FDA Form 1571, a cover sheet for an IND submission, to identify the phase in approximately 10% of all protocols.

  Although 21 CFR 312.21 states that a clinical investigation of a previously untested drug is divided into three phases (1, 2, 3), we included transitional phases (1/2, 2/3, 3/4) to reflect how sponsors categorize protocol submissions.

- Is the protocol indicated for a serious or life-threatening disease or condition? Yes or No

Currently, FDA does not maintain a list of serious or life-threatening diseases and conditions. FDA has defined serious or life-threatening diseases and conditions in previous documents. Most recently, FDA discussed issues related to products intended to treat serious or life-threatening diseases and conditions in the guidance for industry on *Fast Track Drug Development Programs -- Designation, Development, and Application Review* (July 2004)[9]. In conjunction with the CDER Office of Medical Policy and directors of the CDER review divisions, we developed a list of serious and non-serious diseases and conditions for this project. The list includes 120 serious and 72 non-serious diseases and conditions (see appendix H for the list of serious and non-serious diseases and conditions). It was evident from discussions during this project that the seriousness of a disease is often a matter of judgment and can vary by protocol. For example, the seriousness of angina can vary greatly depending on whether it is stable or unstable, new-onset or chronic. For purposes of this project we made a determination as to whether the disease was serious or non-serious and used this one determination for the entire project to ensure consistency (See Chapter 7--Limitations). This list does not have official status for any purposes other than this project.

- Does the study test effectiveness? Yes, No or NS. If the study listed efficacy endpoints as primary or secondary objectives then "yes."

For a complete list of data elements extracted for Compliance Evaluation Program I see appendix I.

[9] http://www.fda.gov/cder/guidance/5645fnl.htm

We also extracted data for a project conducted by the Office of Women's Health (OWH) (see appendix J for a list of the data fields extracted for OWH). The data elements were entered into the database using the OWH Form (see appendix K for a copy of the OWH Form).

C. Quality control

Quality control was conducted on a random sample of 515 protocols, or one out of every four protocols entered into the database, to assure that no more than 10% of the records included an error in any field.

D. Documenting trial listings in ClinicalTrials.gov

NLM prepared weekly reports to provide an update on sponsor trial listings in ClinicalTrials.gov. These reports were used to verify whether IND trials submitted to CDER were being listed in ClinicalTrials.gov. They contained the following: the date the trial was released into ClinicalTrials.gov, sponsor name, official representative's name, IND number, serial number, sponsor protocol ID, NLM identifier, title, condition, and drug name. We used the NLM reports as follows:

- The IND number, serial number, and sponsor protocol ID from the NLM report were compared to data in the OSHI database to verify whether the protocol had been submitted to CDER within the 9-month period of January 1 - September 30, 2002. The comparison process began on January 1, 2002 and continued until March 2004 in order to capture trials with delayed enrollment.

- A final comparison was conducted in March 2004 to verify whether trials meeting the criteria for inclusion in ClinicalTrials.gov (Phase 2, 3, or 4 effectiveness trials for serious or life-threatening diseases and conditions) and contained in the OSHI database were actually listed in ClinicalTrials.gov.

- If the ClinicalTrials.gov trial was in the OSHI database, then the date the trial was listed in ClinicalTrials.gov and the assigned NLM identifier were recorded in the OSHI database (see appendix L for a copy of the Letter Results Form).

- A thank-you letter was e-mailed to the sponsor's official representative acknowledging the listing in ClinicalTrials.gov (see appendix M for a copy of the thank-you letter).

III. Results

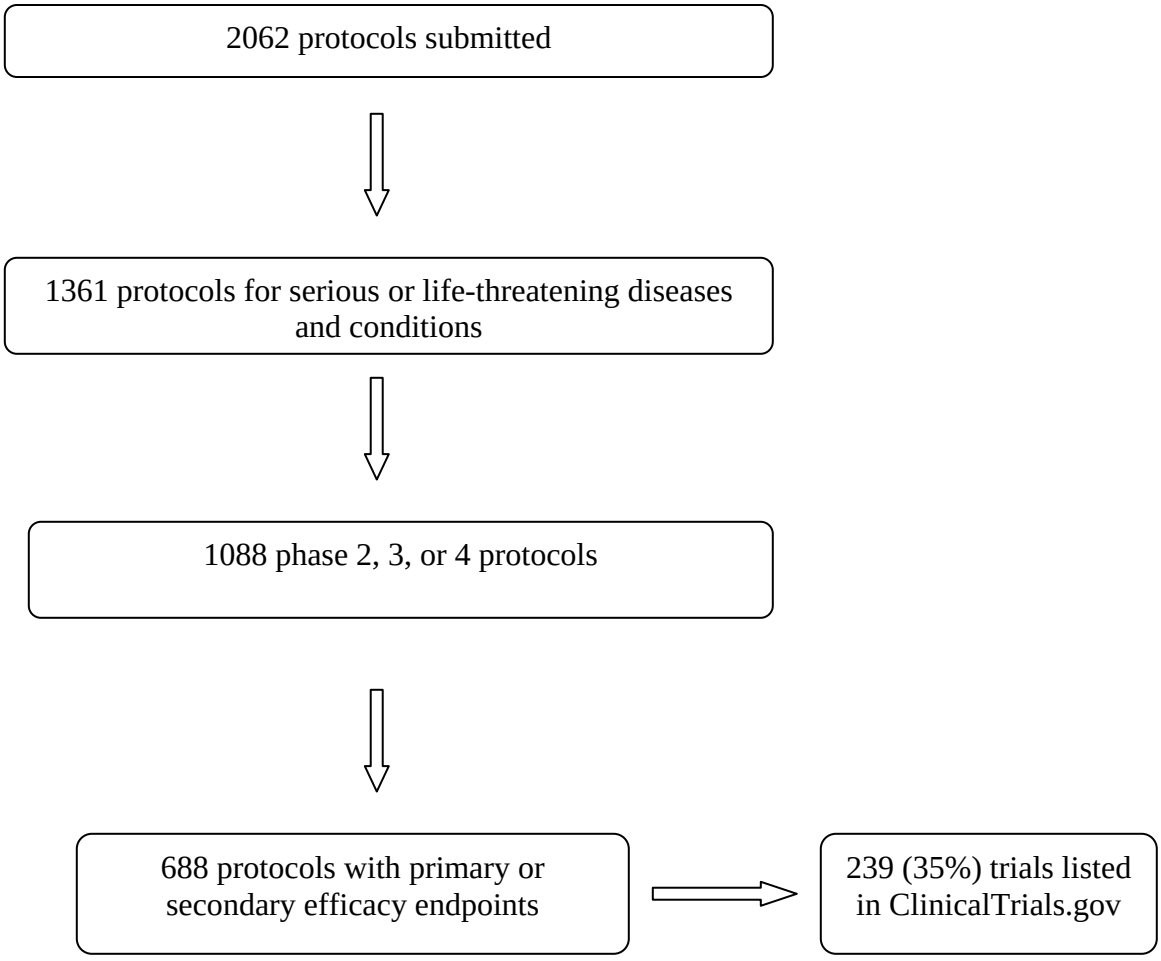
Of the 2,062 protocols submitted to CDER from January 1, 2002 to September 30, 2002 and entered in the OSHI database, we identified 688 protocols that were trials to test effectiveness for serious or life-threatening diseases and conditions and thus met the criteria for inclusion in ClinicalTrials.gov. Sponsors listed 239 (35%) of those 688 trials in ClinicalTrials.gov. Sponsors also listed an additional 35 trials that did not meet the criteria for inclusion.

A. New protocols submitted to CDER and meeting the guidance criteria for listing in ClinicalTrials.gov

A total of 1,865 IND submissions containing 2,062 new commercial protocols were submitted to CDER between January 1, 2002 and September 30, 2002. Of the 2062 protocols submitted, 66% (1361) were for serious or life-threatening diseases and conditions. Of the 1361 protocols for serious or life-threatening diseases and conditions, 80% (1088) were phase 2, 3, or 4 trials. Of the 1088 protocols, 63% (688) had primary or secondary efficacy endpoints and thus met the guidance criteria for submission to ClinicalTrials.gov.

Figure 1 below describes the process used to determine how many protocols met the guidance criteria for listing in ClinicalTrials.gov.

Figure 1. Number of Trials Listed in ClinicalTrials.gov



B. Required trial listings in ClinicalTrials.gov

Thirty-five percent (239/688) of trials that should have been listed in ClinicalTrials.gov, based on our interpretation of FDAMA Section 113 as discussed above, were actually listed. Notably, almost three-fourths of the required phase 3 trials were not listed. Table 1 illustrates within each phase, what proportion of protocols that should have been listed were actually listed in ClinicalTrials.gov.

Table 1. Trial Listings in ClinicalTrials.gov by Phase

Phase	Number of protocols submitted to CDER	Number of protocols required to be listed in ClinicalTrials.gov	Number of protocols listed in ClinicalTrials.gov	Percent of required protocols listed by phase
2	494	314	139	44%
2/3	30	17	8	47%
3	555	303	78	26%
3/4	5	3	1	33%
4	119	51	13	25%
Total	**1203**	**688**	**239**	**35%**

C. Voluntary trial listings in ClinicalTrials.gov

Sponsors are encouraged to list phase 1 trials and/or trials for drugs that are not intended to treat serious or life-threatening diseases and/or are not intended to test effectiveness. Table 2 provides a summary of these voluntary listings by phase.

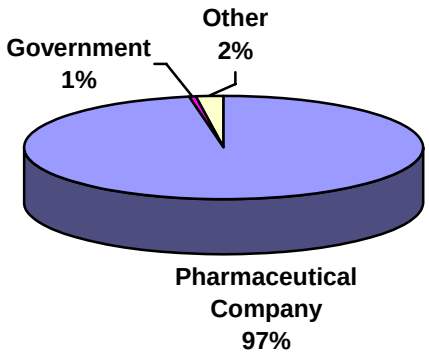
Table 2. Voluntary Trial Listings in ClinicalTrials.gov by Phase

Phase	Number of voluntary trial listings in ClinicalTrials.gov
1	10
1/2	4
2	9
2/3	0
3	8
3/4	1
4	1
Not Specified	2
Total	**35**

D. Sponsor trial listings in ClinicalTrials.gov

We counted the number of sponsors who submitted trials to ClinicalTrials.gov as follows: if the sponsor listed multiple trials at different times during the 9-month period, that sponsor was counted once. Using this approach, 381 sponsors submitted 2062 protocols to CDER during the nine-month period of January 1 - September 30, 2002. Of the 381 sponsors, 370 (97%) were pharmaceutical company sponsors, 3 (1%) were government sponsors (CDC, NIH, or U.S. Army), and 8 (2%) were other (physician or medical center) as shown in Figure 2 below.

Figure 2. Protocols Submitted to CDER by Sponsor Type



As noted in Table 3, about half of the sponsors (187 / 381) submitted at least one protocol that met the criteria for inclusion in ClinicalTrials.gov.

Table 3. Number of New Protocol Submissions by Sponsor

Number of protocols submitted to CDER in 9-month period	Number of sponsors	Number of sponsors who submitted to CDER protocols meeting the criteria for listing in ClinicalTrials.gov
1-5	309	126
6-15	48	37
16-60	19	19
> 60	5	5
TOTAL	**381**	**187**

Of the protocols submitted to CDER that met the criteria for inclusion in ClinicalTrials.gov, NIH listed 90% of their protocols and industry sponsors listed 30% of their protocols. A summary of the findings is presented in Table 4.

Table 4. Compliance by Sponsor Type

Sponsor Type	Total number of protocols submitted to FDA	Trials meeting inclusion criteria	Protocols meeting inclusion criteria and listed in ClinicalTrials.gov
Industry (Pharmaceutical Company)	1934 (94%)	626 (32%)	185 (30%)
Medical Center / University	3 (<1%)	1 (33%)	0 (0%)
NIH	112 (5%)	58 (52%)	52 (90%)
Other Government	5 (<1%)	1 (20%)	0 (0%)
Physician	1 (<1%)	0 (0%)	-----
Other	7 (<1%)	2 (29%)	2 (100%)
Total	**2,062**	**688**	**239**

E. Trial listings in ClinicalTrials.gov sorted by FDA review divisions

The number of trial listings varied by FDA review division. Table 5 illustrates the compliance rate for industry-sponsored trials within each FDA review division. For example, of the submissions to the Division of Antiviral Drug Products by pharmaceutical companies, 50% of the trials that met the criteria for inclusion were listed in ClinicalTrials.gov. For submissions to the Division of Reproductive and Urologic Drug Products, only 4% of the trials that met the criteria for inclusion were listed in ClinicalTrials.gov.

Table 5. Compliance Rate within FDA Review Divisions for Industry-Sponsored Trials

FDA review division	Trials meeting inclusion criteria	Protocols meeting inclusion criteria and listed in ClinicalTrials.gov
Antiviral	32	16 (50%)
Oncology	127	61 (48%)
Anti-Infective	9	4 (44%)
Neuropharmacology	88	32 (36%)
Metabolic/Endocrine	55	15 (27%)
Cardio-Renal	59	14 (24%)
Special Pathogen/Immunologic	22	5 (23%)
Analgesic/Anti-inflammatory/Ophthalmologic	31	6 (19%)
Anesthetic/Critical Care/Addiction	39	6 (15%)
Gastrointestinal/Coagulation	32	4 (13%)
Dermatologic/Dental	21	2 (10%)
Pulmonary	30	2 (7%)
Reproductive/Urologic	28	1 (4%)

IV. Discussion

Pharmaceutical companies listed fewer trials than expected despite a federal law, the issuance of several FDA guidance documents, educational mailings to sponsors, and an easy-to-use web-based data entry tool. Thirty five percent (239/688) of protocols that met the guidance criteria for inclusion in ClinicalTrials.gov were actually listed.

We considered possible reasons why pharmaceutical companies may not have listed trials or may have listed only limited information in ClinicalTrials.gov. The following reasons might explain the low compliance rate:

A) Definition of timing for submissions.
B) Identification of "serious" diseases.
C) Lack of knowledge about the law and/or guidance.
D) Concerns about availability of information to the public and to competitors.
E) Business decisions to stop or delay funding for the development of a specific drug.
F) Identification of trials to test effectiveness.

The first two reasons will be discussed below. The remaining reasons will be discussed as they relate to Compliance Evaluation Program II in the next chapter.

A. Definition of timing for submissions

The March 2002 guidance *Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions* specified that information for existing ongoing trials be submitted to ClinicalTrials.gov within 45 days after the guidance published. Accordingly, ongoing trials meeting the inclusion criteria were to be submitted on or before the implementation date of May 2, 2002. This project included protocols submitted to FDA prior to the implementation date based on the assumption that many studies would still be ongoing on the date of implementation.

We compared pre-implementation data to post-implementation data to assess any differences between compliance rates. For cancer protocols submitted from January 1-May 1, 2002 (pre-implementation), 46% of the protocols submitted by industry to FDA that met the criteria for inclusion in ClinicalTrials.gov were listed in the data bank. Forty-nine percent of the cancer protocols submitted from May 2-September 30, 2002 (post-implementation) by industry that met the criteria for inclusion in ClinicalTrials.gov were listed in the data bank. Although these data are cancer-specific, the data suggest there was little difference in compliance before or after the implementation date of May 2, 2002.

B. Identification of "serious" diseases

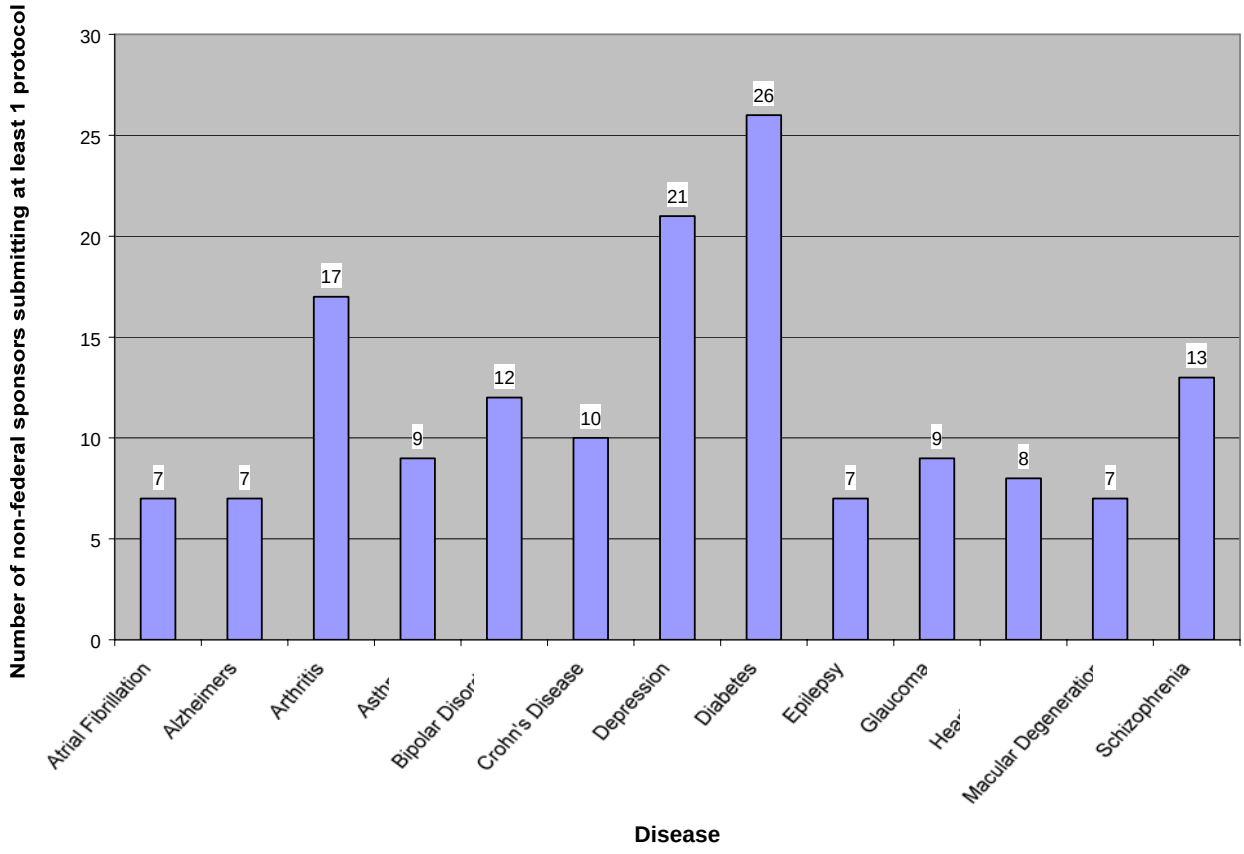
FDA does not maintain a list of serious diseases and conditions to assist sponsors in deciding if a protocol should be listed in ClinicalTrials.gov. However, FDA has defined serious or life-threatening diseases and conditions in previous documents. For example, FDA recently discussed issues related to products intended to treat serious or life-threatening diseases and conditions in the guidance for industry on *Fast Track Drug Development Programs -- Designation, Development, and Application Review* (July 2004).[10] During the study period, it is theoretically possible some companies mistakenly thought only protocols for AIDS and cancer drugs or fast track drugs were required to be listed in the data bank. Indeed, in the guidance *Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions,* fast track drugs are used as an example of the type of drugs that would be considered as intended to treat serious and life-threatening conditions. However, the FDA guidance on Section 113 does not state that *only* fast track drugs need to be included in the ClinicalTrials.gov data bank, and includes a discussion of other diseases or conditions that can be considered serious or life-threatening.[11]

During the study period, it was evident that at least some companies are listing trials for conditions other than AIDS and cancer. We reviewed non-federal trials submitted to ClinicalTrials.gov between May 21, 2001 and November 21, 2003 (n=1100). Figure 3 illustrates the variety of diseases, excluding HIV and cancer, for which non-federal sponsors have submitted trials to ClinicalTrials.gov. For example, 26 different non-federal sponsors listed at least one protocol for diabetes. Trials for depression were listed by 21 different sponsors.

[10] http://www.fda.gov/cder/guidance/5645fnl.htm

[11] Although most of the fast track drugs that have been approved since 1998 have been for cancer or AIDS-related indications, there are many fast track designations that have been granted for a variety of serious diseases. As of December 31, 2004, CDER received 328 fast track designation (FTD) requests. Of these, 77 were denied and 13 were pending action. Of the 238 FTD requests granted, 49% (116/238) were for cancer or AIDS-related indications. The remaining 122 FTD requests granted were for other serious diseases, e.g. Parkinson's Disease, Amyotrophic Lateral Sclerosis, Huntington's Disease, Multiple Sclerosis, Chronic Spinal Cord Injury, Acute Stroke, Acute Pancreatitis, Sickle Cell Disease, Obesity, Complicated Skin Infections, Mucositis, Macular Degeneration, Systemic Lupus Erythematosus, Rheumatoid Arthritis, Osteoarthritis, Cystic Fibrosis, Acute Bacterial Infections, Candidiasis, Aspergillosis, Pneumocystosis, and Congestive Heart Failure. OSHI data on file.

Figure 3. Diseases for which Non-Federal Sponsors have Submitted Protocols



To determine other reasons why sponsors were not listing eligible protocols and to assess more recent compliance with Section 113 of FDAMA, we initiated another project in 2004. Our findings from that project will be presented in Chapter 4.

CHAPTER 4. COMPLIANCE EVALUATION PROGRAM II

In this section, we investigate whether there has been an increase in listing cancer trials in the Clinical Trials Data Bank since 2002. We also investigate additional reasons why sponsors were not submitting trials to the data bank.

I. Objectives

The objectives of the Compliance Evaluation Program II are listed below:

1. To determine the regulatory compliance by comparing the number of cancer trials listed in ClinicalTrials.gov to the number of cancer protocols submitted to CDER's Division of Oncology Drug Products (DODP) during the three-month period of May 1, 2004 and July 31, 2004.[12]

2. To compare the number of cancer trials listed in ClinicalTrials.gov in 2002 versus 2004.

3. To use cancer trials as an example to help determine reasons in general why sponsors are not listing their trials in ClinicalTrials.gov.

II. Methods

New commercial protocols submitted to CDER's DODP between May 1 and July 31, 2004 were identified from a search of the COMIS database. We selected cancer protocols and the May-July timeframe for evaluation for three reasons: 1) cancer is undeniably a serious condition, 2) to update compliance data for cancer that was presented publicly at the April 2003 FDA Science Forum[13] and 3) two years had passed since the May 2, 2002 implementation date.

A. Data collection

Our data collection process in Compliance Evaluation Program II was similar to the process used in Compliance Evaluation Program I.

For a complete description of the data collection process see appendix N.

[12] Cancer protocols are submitted to multiple divisions in CDER. The study was limited to protocols submitted to CDER's Division of Oncology Drug Products, HFD-150.
[13] http://www.cfsan.fda.gov/~frf/forum03/U-04.HTM

B. Data extraction

We used the same data fields in Compliance Evaluation Program II as in Compliance Evaluation Program I, plus the following data fields were added:

- Did the study list primary efficacy endpoints? Yes, No or NS
- Did the study list secondary efficacy endpoints? Yes, No or NS

  If the study listed efficacy endpoints as either primary or secondary, the study was considered to test effectiveness.

- Comments: Insert the name of the sponsor's regulatory affairs person (contact person) responsible for the protocol in the event of follow-up phone calls to the sponsor.

Data were entered into the OSHI database using the Submissions Form (see appendix O for a copy of the Submissions Form). Data extracted during this review were compared to data from May 1 to July 31, 2002.

C. Documenting trial listings in ClinicalTrials.gov

NLM prepared weekly reports to provide an update on sponsor trial listings in ClinicalTrials.gov. The reports were used to verify whether IND protocols submitted to CDER were listed in ClinicalTrials.gov. The NLM reports contained the date the trial was released into ClinicalTrials.gov, sponsor name, official representative, IND number, serial number, sponsor protocol ID, NLM identifier, title, condition, and drug name.

- The IND number, serial number, and sponsor protocol ID from the NLM report were compared to data in the OSHI database to verify whether the protocol had been submitted to CDER within the 3-month period of May 1 - July 31, 2004. The comparison process began on May 1, 2004 and continued until December 31, 2004.

- A final comparison was conducted in January 2005 to verify whether trials contained in the OSHI database met the criteria for inclusion and were listed in ClinicalTrials.gov.

- If the protocol was listed in the OSHI database, the date the trial was listed in ClinicalTrials.gov and the assigned NLM identifier was recorded in the Submissions Form.

D. Follow-up Telephone Calls

Twelve follow-up telephone phone calls were made to sponsors who appeared not to have listed cancer trials that met the criteria for inclusion. The follow-up call was an attempt to gather information about why the sponsor had not listed the trial.

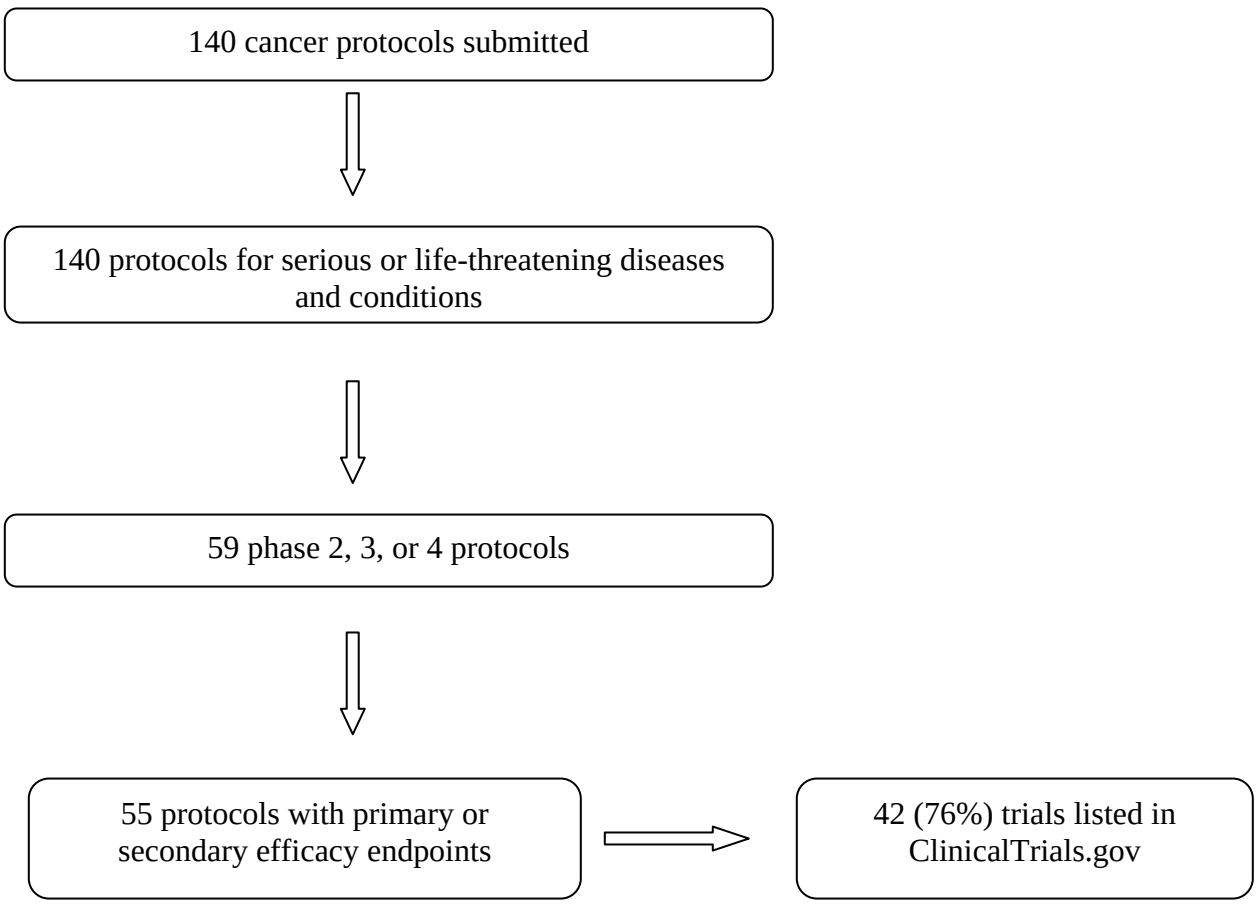
III. Results

A. New protocols submitted to the Division of Oncology Drug Products and meeting the guidance criteria for listing in ClinicalTrials.gov.

One hundred forty commercial protocols were submitted to CDER's DODP between May 1, 2004 and July 31, 2004. Of the 140 cancer protocols, 39% (55) met the criteria for inclusion in ClinicalTrials.gov. Of these 55 trials, sponsors listed 76% of them in ClinicalTrials.gov. Also, sponsors voluntarily listed 19 out of 85 (22%) trials that did not meet the criteria for inclusion.

Figure 4 below describes the process used to determine how many protocols met the guidance criteria for listing in ClinicalTrials.gov.

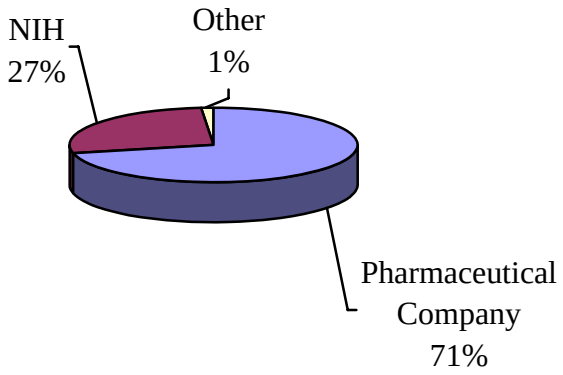
Figure 4. Number of Trials Listed in ClinicalTrials.gov



B. Protocols by sponsor type

Of the 140 cancer protocols submitted to DODP, 100 (71%) were sponsored by pharmaceutical companies, 38 (27%) by NIH, and 2 (1%) by Other*. These results are shown in Figure 5 below.

Figure 5. Protocols Submitted to CDER by Sponsor Type



* Percentage does not add to 100.0 because of rounding.

C. Trial listings in ClinicalTrials.gov by sponsor type

A summary of compliance by sponsor type is presented in Table 6. Of the 55 trials meeting the inclusion criteria, 42 (76%) were listed in ClinicalTrials.gov.

Table 6. Compliance by Sponsor Type

Sponsor Type	Total number of protocols submitted to DODP	Trials meeting inclusion criteria	Trials meeting inclusion criteria and listed in ClinicalTrials.gov
Industry (Pharmaceutical Company)	100	32	21 (66%)
NIH	38	21	20 (95%)
Other	2	2	1 (50%)
Total	**140**	**55**	**42 (76%)**

D. Comparison of 2002 versus 2004 cancer data

When cancer trials submitted in 2004 were compared to those submitted in 2002, compliance increased from 61% to 76%. Table 7 compares the compliance rates by sponsor type.

Table 7. Cancer Trials Submitted to CDER's DODP and Listed in ClinicalTrials.gov (2002 vs 2004)

Sponsor	# Cancer trials listed in ClinicalTrials.gov Jan – Sept 2002	# Cancer trials listed in ClinicalTrials.gov May – July 2002	# Cancer trials listed in ClinicalTrials.gov May – July 2004
Pharmaceutical Company	61 / 127 (48%)	22 / 44 (50%)	21 / 32 (66%) 70%*
NIH/NCI	52 / 57 (91%)	17 / 20 (85%)	20 / 21 (95%)
Other	2 / 3 (66%)	1 / 2 (50%)	1 / 2 (50%) 100%**
TOTALS	115 / 187 (61%)	40 / 66 (61%)	42/ 55 (76%)

* 70% includes trials that were terminated or had delayed enrollment as identified in follow-up telephone calls.

** 100% includes a National Cancer Institute (NCI) cooperative group trial that was submitted to NCI's Physician Data Query (PDQ). There can be a time delay of 4-5 weeks to allow for the trial information to be entered into PDQ then sent to ClinicalTrials.gov.

E. Follow-up telephone calls

Twelve follow-up telephone calls were made to eleven pharmaceutical companies (one company had two protocols) and one sponsor coded as "other" who had trials that met the criteria for inclusion yet could not be located in ClinicalTrials.gov. The following reasons for not listing trials were cited by sponsors:

- Trial was delayed in getting posted due to a vacancy in the clinical study team leader position. (n=1)
- Drug development was terminated. (n=1)
- Enrollment was postponed until first quarter of 2005. (n=1)
- Sponsor had concerns about releasing proprietary information to the public and to competitors. Releasing the information would be detrimental to a small biotech company. (n=1)
- Listing of the trial was overlooked. Trial would be listed as a result of the phone call. (n=3)

- Sponsor acquired the drug from another company. Current sponsor did not verify the listing of the trial by the original sponsor. (n=1)
- Lack of knowledge about the law and guidance. (n=2)
- Sponsor initially intended to have domestic and international trial sites. Domestic sites were never opened and international sites were never listed because accrual was completed by the time of the phone call. (n=1)

The two remaining trials appeared not to be listed in ClinicalTrials.gov for the following reasons:

- A pharmaceutical company-sponsored trial that appeared not to be listed in ClinicalTrials.gov was in fact listed. The FDA investigator misinterpreted the data presented in the ClinicalTrials.gov record. This error occurred because the sponsor did not use the same protocol number in ClinicalTrials.gov as it did in its submission to FDA.

- In another instance, an NCI cooperative group trial was not listed in ClinicalTrials.gov. However, upon follow-up the trial had been submitted through NCI's cancer trial listing, the Physician's Data Query (PDQ) found on Cancer.gov. There can be a time delay of four to five weeks to allow for the trial information to be entered into Cancer.gov then sent to ClinicalTrials.gov.

IV. Discussion

The telephone calls made during Compliance Evaluation Program II confirmed many of our initial thoughts as to why companies were not listing trials. We identified the following reasons, and they are discussed below:

A. Business decisions to stop or delay funding for the development of a specific drug.
B. Lack of knowledge about the law and/or guidance.
C. Identification of trials to test effectiveness.
D. Concerns about availability of information to the public and to competitors.

A. Business decisions to stop or delay funding for the development of a specific drug

We know from discussions with pharmaceutical company representatives that sponsor business decisions may result in a delayed initial trial enrollment date for a protocol submitted to FDA. Sometimes trials are never initiated because funding for the project was discontinued. We expect that these factors accounted for very few of the protocols not listed in Compliance Evaluation Program I because we continued to review trial listings in ClinicalTrials.gov through March 2004, 18 months after we stopped receiving IND submissions. Any delayed trial listings were recorded in the OSHI database and were included in the overall compliance rate. Additionally, we know from the review of 2004 oncology data that only 9% (1/11) of trials not listed could be accounted for by this reason.

B. Lack of knowledge about the law and/or guidance

Very few of the missing trials in the Compliance Evaluation Program I can be explained by lack of knowledge of the law because FDA sent each sponsor a letter specific to the protocol that included information about the law and guidance. FDA mailed 1748 letters to sponsors of protocols submitted to CDER between January 1, 2002 and September 30, 2002. The difference (324) between the total protocols reviewed (2062) and the number of letters sent (1748) is explained by the fact that individual submissions to FDA contained multiple protocols and no letters were sent to NIH. We did not follow-up with sponsors via telephone in Compliance Evaluation Program I as we did in Compliance Evaluation Program II due to the volume of calls that would have been required and the decline in project resources. However, we know from the review of 2004 oncology data that only 18% (2/11) of trials not listed could be accounted for by this reason.

C. Identification of trials to test effectiveness

Although the definition of "effectiveness" was not mentioned in the follow-up telephone calls, we still consider it a possible reason why sponsors are not listing some of their trials. In this study, we considered trials with either primary or secondary efficacy endpoints as trials to test effectiveness.

An example of a possible inconsistency in identifying effectiveness is the following: A sponsor submitted a phase 2 study to evaluate the safety, tolerability and antiviral activity of an investigational drug in HIV-infected children. The primary endpoint was to evaluate the safety and tolerability of the drug. The secondary endpoint was to evaluate the antiviral activity of the drug. FDA identified this trial as a trial to test effectiveness and considered it to have met the guidance criteria for inclusion, however, the sponsor did not list the trial in ClinicalTrials.gov.

For Compliance Evaluation Program I, we did not record how many protocols included primary versus secondary efficacy endpoints and thus cannot estimate the number of missing protocols that could be accounted for by this data element. We modified our database in Compliance Evaluation Program II to include primary and secondary efficacy endpoints. Of the protocols meeting the criteria to be listed in ClinicalTrials.gov (n = 55), 38 had both primary and secondary efficacy endpoints, 13 had primary efficacy endpoints, and four had only secondary efficacy endpoints. Of the four protocols containing only secondary efficacy endpoints, two were listed in ClinicalTrials.gov. For the two trials not in ClinicalTrials.gov, discussions with pharmaceutical company representatives did not suggest the definition of effectiveness as the reason for not listing the trial.

D. Concerns about availability of information to the public and to competitors

We suspect some pharmaceutical companies decided not to list their trials in ClinicalTrials.gov or to list limited information about their trials due to concerns about competitors gaining insight to their drug development plan. We know from the review of 2004 oncology data that 9% (1/11) of trials not listed could be accounted for by this reason. However, the statutory provision mandating the establishment of the data bank does not contain an exception from the requirements for information sponsors consider proprietary. The only ground in either FDAMA 113 or the FDA guidance for not including information about an investigation in the data bank is if a sponsor provides a detailed

certification to the Secretary of HHS that disclosure of such information would substantially interfere with timely enrollment of subjects in the clinical trial. FDA has not identified specific instances when disclosure of information would substantially interfere with enrollment of subjects in a clinical investigation. In the guidance to industry, we solicited comments on this topic for the purpose of including a listing of acceptable reasons for certification. We received no comments and have received no certifications from sponsors.

The issue of making information publicly available raised questions about the validity of this concern and its impact on sponsors' listing of trials to the Clinical Trials Data Bank. To better understand the scope of this concern, we explore some of these issues in the next chapter.

CHAPTER 5: PUBLIC AVAILABILITY OF INFORMATION

In this section, we reviewed the types of information publicly available about the trials that were either not listed in ClinicalTrials.gov or were listed with limited information about the location, drug name, or sponsor name.

I. Trials Not Listed in ClinicalTrials.gov

A. Objective

The objective of this review was to determine what information about drugs in the pipeline is available on the Pharmaceutical Research and Manufacturers of America (PhRMA) website and to compare that information to the information available on ClinicalTrials.gov. PhRMA, a trade organization representing research-based pharmaceutical and biotechnology companies, hosts a New Medicines in Development website at http://www.phrma.org/newmedicines/. According to PhRMA, this website includes treatments under development by and in the pipelines of America's biopharmaceutical companies.

B. Methods

- We conducted reviews at five different times between August 2003 and March 2005: August 2003, January 2004, April 2004, May 2004, and March 2005.[14]

- These reviews captured the following information posted on the PhRMA website and the ClinicalTrials.gov website:

  - drug name
  - sponsor
  - phase
  - drug listing in PhRMA
  - trial listing in ClinicalTrials.gov

- The PhRMA.org website was reviewed to identify drugs under development in phase 2, 3, or 4 for breast cancer, brain cancer, stroke, Parkinson's Disease, and Alzheimer's Disease. PhRMA's website does not list specific trials.

- If the *drug* listed by PhRMA was located in ClinicalTrials.gov as an open or closed study in any phase and conducted by the company or another sponsor (e.g. NIH), then it was considered a trial listed in ClinicalTrials.gov.

- The results were tabulated for comparison.

[14] OSHI data on file

C. Results

Of the five diseases reviewed, pharmaceutical companies listed information about their drugs on PhRMA.org more often than on ClinicalTrials.gov. However, the 2005 review showed an increase in trial listings on ClinicalTrials.gov over those listed in 2003 and 2004 in three of the five diseases (brain cancer, Parkinson's Disease, and Alzheimer's Disease). Table 8 shows the number of drugs listed on PhRMA.org as compared to ClinicalTrials.gov.

Table 8. Drugs Listed in PhRMA.org and ClinicalTrials.gov

	2003		2004		2005	
Disease	**Drugs listed in PhRMA.org (phase 2-4)**	**Drugs listed in ClinicalTrials.gov**	**Drugs listed in PhRMA.org (phase 2-4)**	**Drugs listed in ClinicalTrials.gov**	**Drugs listed in PhRMA.org (phase 2-4)**	**Drugs listed in ClinicalTrials.gov**
Breast Cancer	30	23 (77%)	27	19 (70%)	21	15 (71%)
Brain Cancer	12	7 (58%)	9	6 (67%)	6	6 (100%)
Stroke	N/A	N/A	11	6 (55%)	10	5 (50%)
Parkinson's Disease	N/A	N/A	17	7 (41%)	13	11 (88%)
Alzheimer's Disease	N/A	N/A	15	5 (33%)	15	10 (67%)

N/A: Diseases were not reviewed during the specified year.

D. Discussion

It is possible that a trial for the drug listed in PhRMA.org existed in ClinicalTrials.gov but the investigator was unable to find it because the sponsor chose not to list the specific drug name in ClinicalTrials.gov (see Section II below).

II. Trials Listed in ClinicalTrials.gov with Limited Information about Location and Contact Information, and Drug and Sponsor Name

There are three data fields for which some companies provided limited information for listed trials. These fields are location, drug name, and/or sponsor name. We will discuss the review of each field separately below.

A. Location and Contact Information

1. Objective

The objective of this review was to determine what types of information sponsors submitted to ClinicalTrials.gov to describe the study location and contact information.

2. Methods

- Between July 2002 and August 2004 FDA sent 23 letters to sponsors via e-mail referencing a total of 68 trials listed in ClinicalTrials.gov that did not list trial site locations (see appendix P for a copy of the letter sent to sponsors). In September 2004, NLM assumed the role of sending the letters electronically.

- In the letter, specific trials were referenced, and sponsors were asked to include the city, state, and country for each clinical trial site so that visitors to ClinicalTrials.gov could search for clinical trials by location.

- We retrospectively sampled records four times during the following periods to review location and contact information: October 2003, September and December 2004, and March 2005.

    - In October 2003, we randomly sampled 100 records listed in ClinicalTrials.gov between August 2001 and September 2003.

    - We reviewed all new trial records entered in ClinicalTrials.gov for the following months:
        - May 2004 (n = 33)
        - August 2004 (n = 64)
        - January 2005 (n = 53)

    - We determined if the sponsor listed the following location information:
        - Institution where the trial was being conducted
        - City and state where the trial was being conducted
        - Principal investigator was identified

    - We determined if the sponsor listed the following contact information:
        - Local telephone number
        - Central telephone number (800 number for a clinical trial call center)
        - Both a local and central contact number
        - Did not list a telephone number

3. Results

Table 9 shows greater than 90 percent of sponsors listed the trial site's city and state, but less than half listed the name of the institution and principal investigator. Approximately one-half to two-thirds of sponsors chose to list a central contact telephone number rather than a local telephone number.

Table 9. Location and Contact Information Listed by Pharmaceutical Companies

N/A: Investigator reviewed trials for local telephone number only.

Data Element	Percent of Trials Listed October 2003 (n = 100)	Percent of Trials Listed May 2004 (n = 33)	Percent of Trials Listed August 2004 (n = 64)	Percent of Trials Listed January 2005 (n = 53)
LOCATION				
Institution	64%	73%	40%	42%
City and State	93%	100%	95%	91%
Principal Investigator	45%	48%	30%	30%
CONTACT NUMBER				
Local	40%	27%	33%	36%
Central	N/A	42%	54%	64%
Both	N/A	12%	5%	13%
None	N/A	18%	8%	13%

4. Discussion

In accordance with Section 113 of FDAMA, sponsors are required to list the location of the trial and contact information for all trial sites listed in ClinicalTrials.gov. Location of the trial is important information for patients. Some patients are willing and able to travel anywhere to participate in a study, but others are unwilling or unable to travel. Those in the latter group can limit their searches

to locations to which they can travel. Initially, sponsors were asked to include in the trial record the name of the institution where the clinical trial was to be conducted. Some companies chose to list the city and state but not the institution name. Some companies chose to list an 800 telephone number only without listing any location information.

The PRS data fields were modified to reflect that an adequate description of the trial site location would consist of the city and state for each trial site and recognize that from a patient perspective, one cannot discern the trial site location from an 800 number. For example, if a patient conducted a search for asthma trials and 40 trials appeared with only 800 numbers listed and no location, the patient would possibly have to make 40 individual phone calls to determine each trial's location.

B. Drug Name and Sponsor Name

1. Objectives

The objectives of this section were as follows:

- To determine to what extent sponsors listed their company names or drug names for trials listed in the Clinical Trials Data Bank.

- To determine what information was publicly available for trials without drug names listed in the Clinical Trials Data Bank.

2. Methods

1) To determine the extent of company and drug names listed in ClinicalTrials.gov, we reviewed all protocols submitted by pharmaceutical companies between May 2001 and February 2004 (n=1220). We identified trials whose sponsors listed "investigational drug" instead of the drug name and "pharmaceutical company" instead of the actual company name.

2) To determine the availability of public information for trials without drug names listed, we conducted two reviews in 2002 and 2004 as follows:[15]

   - In 2002, we reviewed the names for seven drugs listed as "Investigational Drug" in ClinicalTrials.gov.

   - In 2004, we reviewed the names of twelve drugs listed as "Investigational Drug" in ClinicalTrials.gov, of which six were FDA approved drugs and six were investigational drugs.

   - Searches were conducted using the drug name on the company website, PhRMA.org, Google.com, and competitive intelligence websites.

[15] OSHI data on file

3. Results

In the 2002 search for publicly available information about trials listed without drug names, six of seven drugs were found on the companies' websites. Most of the information was found in the annual report or investor materials section of company websites. More detailed information could be obtained from other websites for a fee.

In the 2004 search, results were similar to those in 2002. Each of the twelve drugs was identified in at least one of the sites mentioned above.

In the February 2004 review to evaluate to what extent sponsors listed their company names or drug names in ClinicalTrials.gov, we found that five pharmaceutical companies did not list their company name and nine companies did not list their drug name in ClinicalTrials.gov. Further analysis showed the following:

- 112 out of 1,220 (9%) trials did not contain drug name (e.g. “Investigational New Drug” used instead).

- 96 out of 1,220 (8%) trials did not contain company name (e.g. “Pharmaceutical Company” used instead).

Of the trials mentioned above, 80 omitted both company name and drug name.

4. Discussion

Some sponsors did not list their company name and/or drug name for some or all trials. Instead they listed "Pharmaceutical Company" or "Investigational New Drug" in the sponsor name and drug name data fields.

Information about the drug name and company name could be important to patients. For example, if a patient learns about a new cancer treatment on the evening news, she might remember the name of the drug or the name of the company investigating the drug. In either situation, if the patient searched by the drug name or company name in ClinicalTrials.gov, she would not find it if the sponsor had not provided this information.

Based on the results of the reviews, it is evident that even if a drug's name is not disclosed on ClinicalTrials.gov, it generally is available on publicly-accessible websites.

Patients are the most likely population to benefit from having the drug and company names available to them when searching ClinicalTrials.gov. Competing companies and investors already have access to extensive information about investigational drugs through general Internet searching and purchasing information from subscription databases such as Biospace's Clinical Competitive Intelligence System (CCIS) or for a one-time fee-per-information packet. Futhermore, it is consistent with the intent of ClinicalTrials.gov for this information to be available to patients in one

location, rather than their having to search multiple websites and attempt to collate disparate information.

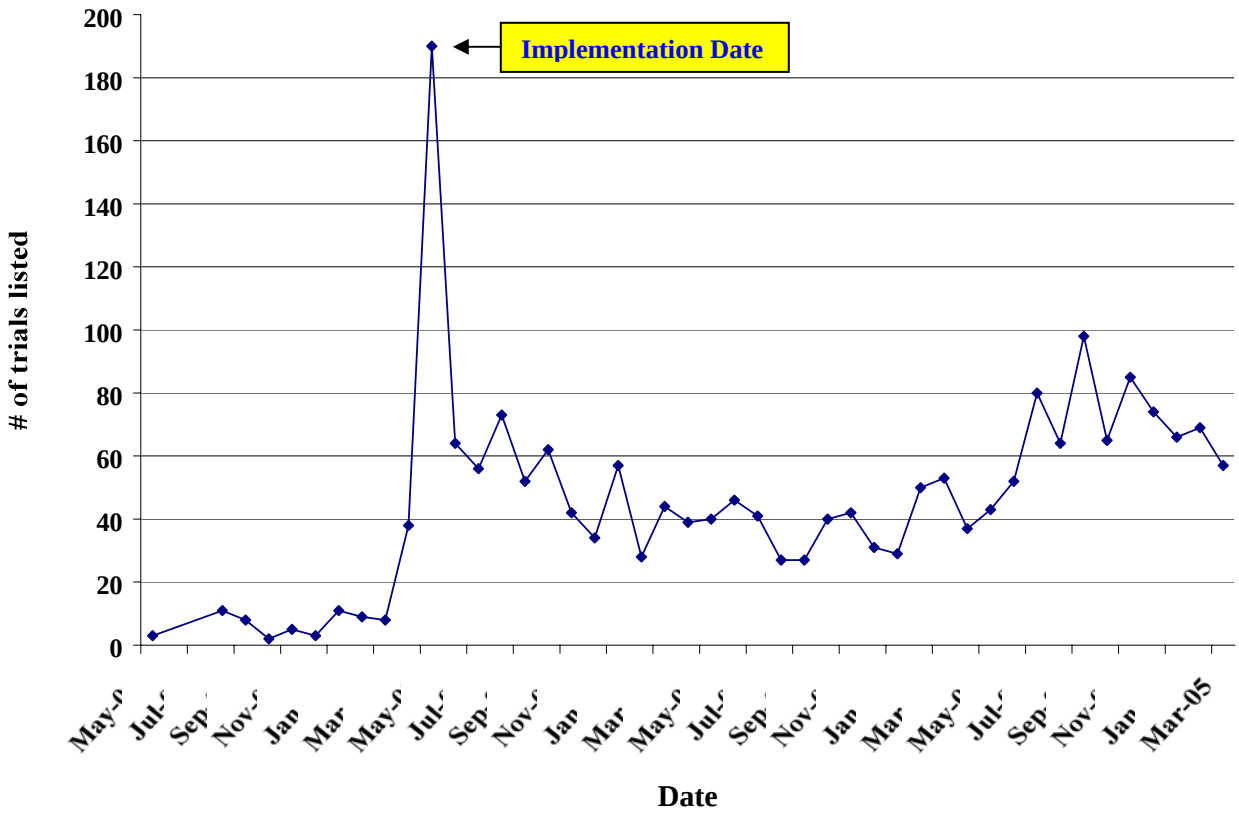
In the fall of 2004 it became evident that sponsors were modifying their practices with regard to listing drug and sponsor names in the data bank; by December 31, 2004, the major pharmaceutical companies were listing their company names, and it appeared that only one major pharmaceutical company routinely continued to not list drug names. It also appears that some companies continue to make case by case decisions to not list drug names.

C. 2004 Update

The National Library of Medicine provides us with a list of trials submitted to ClinicalTrials.gov each week by non-federal sponsors. From the list we are able to monitor the trend in the number of trials submitted on a monthly basis.

Figure 6 shows that in the first two years after implementation (June 2002 through May 2004), an average of 44 trials/month were listed. Since June 2004, an average of 71 trials per month were listed. In the summer of 2004, media and congressional attention to issues related to the public availability of clinical trial information may have heightened awareness about ClinicalTrials.gov.

Figure 6. Monthly Trial Listings in ClinicalTrials.gov by Non-Federal IND sponsors



Similarly, the results from Compliance Evaluation Program II compared to the results from Compliance Evaluation Program I showed about a twenty percent increase in compliance (50% to 69%) for non-federal sponsors.

We hope that compliance will continue to increase. In addition to continued media and congressional attention to this topic, on January 6, 2005, PhRMA issued a press release about its new *voluntary* disclosure policy, "Pharmaceutical Companies to Make More Information Available About Clinical Trials." Under this policy PhRMA member companies should provide information about clinical trials for all diseases, not only for serious or life-threatening diseases. The policy states that information about new hypothesis-testing trials will be posted on ClinicalTrials.gov on a voluntary basis beginning July 1, 2005, and ongoing hypothesis-testing trials are to be posted by September 13, 2005.

CHAPTER 6. REPORTING CLINICAL TRIAL RESULTS IN THE CLINICAL TRIALS DATA BANK

Recent public attention has focused on expanding public access to information about *results* of clinical trials. Proposals for establishing results databases have been offered and/or implemented by a variety of organizations, such as the American Medical Association,[16] National Institutes of Health,[17] International Committee of Medical Journal Editors,[18] the US Congress,[19] the World Health Organization,[20] PhRMA,[21,22,23] and individual pharmaceutical companies.[24, 25] FDAMA 113 provides for including information pertaining to the results of clinical trials, with the consent of the sponsor.

This chapter explores issues around clinical trial results and other information submitted by sponsors to the Clinical Trials Data Bank.

Background

Currently, there is no Congressionally-mandated data bank for *results* of clinical trials. Listing results of clinical trials in ClinicalTrials.gov is voluntary. In order to provide sponsors with a mechanism to reference results, ClinicalTrials.gov created a general *More Information* (formerly called *Related Information*) data element field. Sponsors can provide *References*, defined as citations to publications related to the protocol such as background and/or results. Sponsors provide either unique PubMed Identifier (PMID) of an article or enter the full bibliographic citation.

In October 2004, ClinicalTrials.gov was updated to include a specific *Results Reference* data element field to allow sponsors to indicate if the reference provided reports on results from the referenced clinical research study.

The *More Information* data element field also includes an option to provide other *Links*, defined as a Web site directly relevant to the protocol. It specifies that links should not include sites whose primary goal is to advertise or sell commercial products or services. Links to educational, research, government, and other non-profit Web pages are acceptable. All submitted links are subject to review by ClinicalTrials.gov.

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[16] June 2004 http://www.ama-assn.org/ama/pub/category/14314.html
[17] September 2004 http://www.nih.gov/about/publicaccess/index.htm
[18] September 2004 ICMJE announces clinical trials must be listed in a public trials registry to be considered for publication http://www.icmje.org/clin_trial.pdf and May 2005 http://www.icmje.org/clin_trialup.htm.
[19] October 2004 Kennedy/Dodd Bill S 2933 Draft and Markey/Waxman F.A.C.T. Bill HR 5252 Draft
[20] October 2003, November 2004 http://www.who.int/rpc/meetings/en/WHO2.pdf and April 2005 WHO technical consultation on clinical trial registration standards meeting http://www.who.int/ictrp/news/ictrp_sag_meeting_april2005_conclusions.pdf
[21] June 2004 PhRMA updates principles for communication of clinical trial results and conduct of clinical trials http://www.phrma.org/publications/publications//2004-06-30.1035.pdf
[22] September 2004 PhRMA announcement of central database presenting results of clinical studies of marketed drugs. http://www.phrma.org/mediaroom/press/releases/07.09.2004.1063.cfm
[23] January 2005 Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases and related information. http://www.phrma.org/mediaroom/press/releases/06.01.2005.1112.cfm and http://www.phrma.org/mediaroom/press/releases/06.01.2005.1114.cfm
[24] December 2004 http://www.lillytrials.com/
[25] September 2004 http://ctr.gsk.co.uk/welcome.asp

I. Objectives

The objectives of this review were to determine the following:

- Which citations to publications related to the protocols sponsors listed in ClinicalTrials.gov
- To what extent publication citations (referred to as References) were available at no cost and as full-text
- What types of links to websites did sponsors list in ClinicalTrials.gov
- To what extent the links listed by sponsors contained promotional material.

II. Methods

A. References

- NLM staff identified all records submitted through the PRS by non-federal sponsors through October 2004 (n=1768).
- We reviewed each record via searches of the publicly accessible ClinicalTrials.gov website to determine the type of information being posted and if the information was available as no-cost, full-text articles.
- Information was categorized into 14 categories (see Table 10).
- Data were entered in a Microsoft Excel spreadsheet. References were further evaluated through PubMed abstracts. For several references, their category was defined by PubMed and listed at the bottom of the PubMed abstract. References without a PubMed category were reviewed and categorized.
- The references were reviewed to determine the availability of the information as no-cost, full-text articles.

Table 10. Categories of References

Clinical Trials	Animal Studies
Human Studies	Review Articles
Case Reports	Letters
Editorials	Cellular/Biological Studies
Evaluation Studies	Textbooks
Data Reports	Practice Guidelines
Informative Articles	Other (not yet classified)

B. Links

- NLM staff identified all records submitted through the protocol registration system (PRS) by non-federal sponsors through October 2004 (n=1768).

- We reviewed each record on ClinicalTrials.gov to assess what types of links were being listed and to assess whether the links contained promotional material.
- The links were reviewed for promotional content. Only studies that were currently recruiting were evaluated (n = 111).

III. Results

A. References

Seventy-six records (4%) were identified as having posted references in the *More Information* data field. Of the 76 records, 66 were for unique interventions (drug, device, or biologic). The 76 records contained 358 references and were listed by 44 unique non-federal sponsors. Of the 358 references reviewed, 34.6% described human drug studies. Other commonly referenced materials included animal studies (21.8%), review articles (11.7%), and human studies not using drugs (11.2%). The remaining 20.7% of the references cited a variety of other types of information such as editorials, case reports, correspondence, textbooks, and practice guidelines. Of the 358 references reviewed, 177 (49%) were available as full-text. Of these, half (85) were available at no cost. Many important medical journals make available online, free and full text articles and release some or all of their content 6-12 months after publication. We did not identify the time at which free access was available for each journal publication nor did we do a search to determine which completed studies had results published.

B. Links

One-hundred records were identified as having posted links in the *More Information* data field. The 100 records contained 139 links consisting of 78 unique sites and 61 duplicates. Approximately half (51%) of the links were to sponsors' websites. The remaining links were to clinical trial search engines (18%), trial sites (14%), nonprofit sites (9%), government sites (4%), drug sites (3%), and research facility sites (1%). A preliminary review by OSHI found none of the links contained promotional material. We did not have access to information about these products sufficient to assess whether information in these sites was selectively presented or otherwise misleading with respect to evidence of safety or efficacy of products discussed. However, we found no links to information that appeared overtly promotional, necessitating referral to FDA/CDER Division of Drug Marketing, Advertising and Communication or the CBER Office of Compliance and Biologics Quality.

CHAPTER 7. LIMITATIONS

The limitations of Evaluation Programs I and II are listed below:

Compliance Evaluation Program I

- The study reviewed protocol listings for applications submitted to CDER during a nine-month period in 2002. Although no CBER protocols were reviewed, we expect the results for CBER applications would be similar.

- As part of Compliance Evaluation Program I, FDA did not contact IND sponsors to inquire why protocols that FDA determined to meet the criteria for inclusion were not included in ClinicalTrials.gov. This was due to the volume of calls that would have been required and the decline in resources.

- FDA does not maintain a list of serious diseases and conditions to assist sponsors in deciding if a protocol should be listed in ClinicalTrials.gov. It was evident from discussions during this project that the seriousness of a disease is often a matter of judgment and can vary by protocol. For example, the seriousness of angina can vary greatly depending on whether it is stable or unstable, new-onset or chronic. In order to ensure consistency in how we coded each protocol, it was necessary to create a list of serious and non-serious diseases and conditions. This list does not have official status for any purposes other than this project.

    - There were eight diseases that we considered serious for purposes of this project that could have been considered non-serious. We analyzed the data using both classifications. If we would have considered the eight diseases non-serious, sponsor participation would have increased from 33% to 37%.

- We were unable to retrieve 24 paper IND submissions. We do not expect these missing documents would impact the overall study results.

- We were unable to identify the phase in six percent (127/2,062) of the protocols submitted to CDER. If the phase was not specified, we did not consider it a trial required to be listed in ClinicalTrials.gov even if it was for a serious disease and tested effectiveness.

- Due to resource limitations we limited the timeframe for data collection to nine months. We do not expect that three additional months of data would impact the overall study results for Compliance Evaluation Program I.

Compliance Evaluation Program II

- Due to resource limitations we limited the timeframe for data collection to three months. We selected the timeframe of May-July in order to reflect the potential increase in trial listings due to the heightened awareness about ClinicalTrials.gov. Because of increased attention to issues related to the public availability of clinical trial information, it is possible, but not likely, that overall compliance for twelve months would have increased had we reviewed twelve months of data instead of three months.

Compliance Evaluation Programs I and II

- The studies reviewed only commercial protocols submitted to FDA during the study timeframes. We recognize that protocols coded *research* may have met the criteria for inclusion in ClinicalTrials.gov; however, due to limited resources we chose to review only commercial protocols.

- We coded trial phase by using the protocol synopsis or the protocol title. If phase was not listed in either of these sections, we used the phase listed by the sponsor on the FDA Form 1571. It is possible that these phase listings were not always correct. We estimate that phase was identified using Form 1571 in approximately 10% of the protocols.

- Some draft protocols were coded as new protocols (PN) in COMIS. We did not include these protocols in the studies. However, it is possible that some protocols that were submitted as draft protocols were not easily identified as a draft. These protocols would not have been required to be listed in ClinicalTrials.gov.

- Multiple steps were taken to verify trial listings in ClinicalTrials.gov. It is possible that a listing could have been missed if serial numbers in the OSHI database and ClinicalTrials.gov didn't match and:

    - Sponsors used different protocol numbers for FDA submissions and ClinicalTrials.gov submissions.

    - Final versions of the protocols submitted after September 30, 2002 were not identified.

CHAPTER 8. SUMMARY

The Department of Health and Human Services developed ClinicalTrials.gov in response to legislation calling for a publicly-accessible registry of clinical trials for serious or life-threatening diseases and conditions. Compliance with the legislation has been mixed. While progress has been made, participation by the pharmaceutical industry is less than expected despite a federal law, a final guidance document, a targeted education program, and an easy-to-use web-based data entry tool. Some pharmaceutical companies do not provide required clinical trials, some provide only limited information, while others voluntarily list trials that go beyond the criteria specified in the guidance.

There has been progress on implementing the legislation, however more needs to be done by FDA, pharmaceutical companies, and others to assure increased participation in ClinicalTrials.gov.

- FDA should further clarify messages about which trials and what information should be listed in ClinicalTrials.gov. We have updated IND acknowledgement letter templates to include a new paragraph reminding sponsors of their responsibility to comply with Section 113 of FDAMA and encouraging the listing of all trials. We will update the Guidance for Industry *Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions* to reflect the findings from our study.

- Pharmaceutical companies and other private sector sponsors are encouraged to review their systems for identifying and submitting protocols to ClinicalTrials.gov. We expect that the number of industry-sponsored trials submitted to ClinicalTrials.gov over the next six months will continue to rise as a result of a recent PhRMA initiative and public awareness and scrutiny. Under a new voluntary disclosure policy announced in January 2005, PhRMA members have agreed to provide information about ongoing hypothesis-testing trials for *all* diseases to ClinicalTrials.gov by September 13, 2005. The policy also encourages PhRMA member companies to establish and make public procedures for verifying compliance with the policy. In addition, the ICMJE announced their position that trials must be registered in order to be considered for publication. New trials will be required to be registered starting July 1, 2005 and ongoing trials must be registered by September 13, 2005.

- Patient advocacy groups should continue to be proactive in encouraging FDA and pharmaceutical companies to make information about ongoing trials more available through ClinicalTrials.gov. Advocacy group initiatives like the Kidney Cancer Association's policy to not list a clinical trial on its website unless the trial is listed in ClinicalTrials.gov are commendable.

The collection and dissemination of information about clinical trials and their outcomes is an important consumer and health practitioner issue. FDA will continue to encourage sponsors to put required and voluntary information into ClinicalTrials.gov. We believe a comprehensive clinical trials database can lead to more efficient and timely discovery of the answers to scientific questions that will result in more quickly learning about the safety and efficacy of treatments for patients. FDA welcomes a continued dialogue on the type of information from clinical trials that would be useful to patients, families, and providers to facilitate their making better informed treatment

decisions. Comments can be submitted via email to the Office of Special Health Issues at 113trials@oc.fda.gov or by mail to Director, Office of Special Health Issues, Office of External Relations, Office of the Commissioner, HF-12, 5600 Fishers Lane, Rockville, MD 20857.

APPENDICES

APPENDIX A

Appendix A: Acronyms & Definitions

CDER	Center for Drug Evaluation and Research
CBER	Center for Biologics Evaluation and Research
COMIS	Center ORACLE Management Information System
DODP	Division of Oncology Drug Products
FDAMA	Food and Drug Administration Modernization Act
HHS	Health and Human Services
IND	Investigational New Drug Application
NCI	National Cancer Institute
NIH	National Institutes of Health
NLM	National Library of Medicine
OSHI	Office of Special Health Issues
OWH	Office of Women's Health
PDQ	Physician's Data Query
PhRMA	Pharmaceutical Research and Manufacturers of America
PRS	Protocol Registration System

Active IND	An IND that is not in clinical hold, inactive, withdrawn, or terminated status.
Commercial IND	An IND for which the sponsor is usually a corporate entity. Other INDs may be designated as commercial if it is clear the sponsor intends the product to be commercialized at a later date. INDs from the National Institutes of Health (NIH) will not be classified as commercial INDs until such time as the division determines that commercial development is being pursued.
COMIS	A CDER electronic management information system.
Fast Track Products	New drugs that are intended to treat serious or life-threatening conditions and that demonstrate the potential to address unmet medical needs.
Industry	Pharmaceutical companies
Research IND	An IND for which the sponsor is usually an individual investigator or an academic institution. Other INDs may be designated as research if it is clear the sponsor does not intend for the product to be commercialized at a later date. INDs from the National Institutes of Health (NIH) will be classified as research INDs until such time as the division determines that commercial development is being pursued.
Sponsor	An individual or pharmaceutical company, governmental agency, academic institution, private organization or other organization who takes responsibility for and initiates a clinical investigation.

Appendix B: CDER Letter Template

SPONSOR'S NAME
Attention: NAME OF CONTACT PERSON, TITLE
SPONSOR'S ADDRESS

Dear NAME:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for NAME OF DRUG.

We also refer to your amendment(s) dated DATE(S), serial number(s) NUMBER(S), containing information about a new protocol.

The purpose of this letter is to inform you about the Clinical Trials Data Bank available to the public through the Internet at http://clinicaltrials.gov. The National Institutes of Health (NIH) through its National Library of Medicine (NLM), and with input from the FDA and others, developed the Clinical Trials Data Bank, as required by the Food and Drug Modernization Act of 1997 (Modernization Act).

Section 113 of the Modernization Act amends 42 U.S.C. 282 and requires the establishment of a public resource for information on studies of drugs for serious or life-threatening diseases conducted under FDA's Investigational New Drug (IND) regulations (21 CFR part 312). It directs the Secretary of Health and Human Services, acting through the Director of NIH, to establish, maintain, and operate a data bank of information on clinical trials for drugs for serious or life-threatening diseases and conditions.

The Clinical Trials Data Bank is intended to be a central resource, providing current information on clinical trials to individuals with serious or life-threatening diseases, other members of the public, healthcare providers, and researchers. Specifically, the Clinical Trials Data Bank will contain 1) information about clinical trials, both federally and privately funded, of experimental treatments for patients with serious or life-threatening diseases; 2) a description of the purpose of each experimental drug; 3) patient eligibility criteria; 4) the location of clinical trial sites, and 5) a point of contact for those wanting to enroll in the trial. This information must be submitted if the clinical trial concerns a serious or life-threatening disease or condition and if the trial tests effectiveness.

FDA has made available a final guidance to implement Section 113 of the Modernization Act. The guidance describes the type of information to submit and how to submit information about clinical trials for serious or life-threatening diseases or conditions to the Clinical Trials Data Bank.

The guidance entitled "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions" was made available on March 18, 2002. It is accessible through the Internet at http://www.fda.gov/cder/guidance/4856fnl.htm

The data fields and their definitions are available in the Protocol Registration System at http://prsinfo.clinicaltrials.gov/. Protocols listed in this system will be made available to the public on the Internet at http://clinicaltrials.gov.

Please review the referenced protocol to determine if it is a trial for a serious disease or condition and if it is a trial to test effectiveness. If the protocol meets these criteria, you must submit information about the trial to the Clinical Trials Data Bank, unless you provide detailed certification to FDA that such a disclosure would substantially interfere with the timely enrollment of subjects in the investigation (42 U.S.C. 282(j)(3) and (j)(4)). You can also submit information about clinical trials under IND that do not meet the criteria described in the Modernization Act.

We appreciate your cooperation. This project is a collaborative effort by the FDA Office of Special Health Issues, the FDA Center for Drug Evaluation and Research (CDER), and NLM/NIH. You will receive a similar letter for each new protocol submitted to a CDER IND during 2002. If you have any questions, contact Theresa Toigo or Janelle Derbis in the Office of Special Health Issues at (301) 827-4460 or e-mail at 113trials@oc.fda.gov.

Sincerely,

{See appended electronic signature page}

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

{See appended electronic signature page}

Theresa Toigo, R.Ph., M.B.A.
Director
Office of Special Health Issues
Office of Communications and Constituent Relations
Office of the Commissioner

Appendix C: CDER Education Program

- OSHI staff photocopied the FDA Form 1571 for each IND. This form contains the most current mailing address for the sponsor or sponsor's authorized representative.

- Letters were created no sooner than 37 days after the stamp date (the date FDA received the submission) recorded on the paper IND to ensure after 30 days the protocol was not subject to clinical hold. Letters were created electronically on a weekly basis using COMIS PE, a CDER management information system.

- OSHI created a standard letter template containing protocol-specific fields. (see appendix B). COMIS PE electronically input the protocol-specific information into the letter template. Information such as the sponsor's name, address, and drug name was verified and updated as needed using a paper copy of FDA Form 1571.

- Letters were logged into the paperless Document Filing System (DFS). Through DFS, each letter was reviewed and signed electronically by the Director of CDER and the Director of OSHI or their designees. The project manager received a signed electronic copy of the letter.

- Letters were sent via U.S. mail to sponsors by the CDER division document room.

OSHI made two attempts to obtain all paper INDs. A total of 24 paper INDs were not received. If the paper IND was not received, a letter was not sent to the sponsor.

Appendix D: CBER Letter Template

SPONSOR
Attention: FIRST_NAME, MIDDLE, LAST_NAME, CREDENTIAL
TITLE
Addess1
Adress2
Address3, City, State, Country

Dear Sponsor:

Please refer to your Investigational New Drug Applications (INDs) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act referenced in the enclosure.

The purpose of this letter is to inform you about the Clinical Trials Data Bank available to the public through the Internet at http://clinicaltrials.gov. The National Institutes of Health (NIH) through its National Library of Medicine (NLM), and with input from the FDA and others, developed the Clinical Trials Data Bank, as required by the Food and Drug Modernization Act of 1997 (Modernization Act).

Section 113 of the Modernization Act amends 42 U.S.C. 282 and requires the establishment of a public resource for information on studies of drugs for serious or life-threatening diseases conducted under FDA's Investigational New Drug (IND) regulations (21 CFR part 312). It directs the Secretary of Health and Human Services, acting through the Director of NIH, to establish, maintain, and operate a data bank of information on clinical trials for drugs for serious or life-threatening diseases and conditions.

The Clinical Trials Data Bank is intended to be a central resource, providing current information on clinical trials to individuals with serious or life-threatening diseases, other members of the public, healthcare providers, and researchers. Specifically, the Clinical Trials Data Bank will contain 1) information about clinical trials, both federally and privately funded, of experimental treatments for patients with serious or life-threatening diseases; 2) a description of the purpose of each experimental drug; 3) patient eligibility criteria; 4) the location of clinical trial sites, and 5) a point of contact for those wanting to enroll in the trial. This information must be submitted if the clinical trial concerns a serious or life-threatening disease and if the trial tests effectiveness.

FDA has made available a final guidance to implement Section 113 of the Modernization Act. The guidance describes the type of information to submit and how to submit information about clinical trials for serious or life-threatening diseases or conditions to the Clinical Trials Data Bank. The guidance entitled "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions" was made available on March 18, 2002. It is accessible through the Internet at http://www.fda.gov/cber/gdlns/clintrial.pdf.

The data fields and their definitions are available in the Protocol Registration System at http://prsinfo.clinicaltrials.gov/. Protocols listed in this system by industry sponsors will be made available to the public on the Internet at http://clinicaltrials.gov.

Please review your protocol(s) to determine if it is a trial for treatment of a serious disease or condition and if it is a trial to test effectiveness. If the protocol(s) meets these criteria, you must submit information about the trial to the Clinical Trials Data Bank, unless you provide detailed certification to FDA that such a disclosure would substantially interfere with the timely enrollment of subjects in the investigation (42 U.S.C. 282(j)(3) and (j)(4)). You can also submit information about other clinical trials under IND.

We appreciate your cooperation. If you have any questions, contact Theresa Toigo or Janelle Derbis in the Office of Special Health Issues at (301) 827-4460 or e-mail at 113trials@oc.fda.gov.

Sincerely,

Kathryn C. Zoon, Ph.D.
Director
Center for Biologics Evaluation and Research

Theresa Toigo, R.Ph., M.B.A.
Director
Office of Special Health Issues
Office of Communications and Constituent Relations
Office of the Commissioner

APPENDIX E

Appendix E: CBER Education Program

- CBER provided OSHI with a database containing information on all active IND holders. Information included IND number, sponsor's name and address, and name of the biologic.

- Contact information from the CBER database was merged into the letter template (see appendix D).

- Each letter contained an attachment referencing each active IND held by the sponsor.

- Letters were sent via U.S. mail to sponsors.

Appendix F: Compliance Evaluation Program I: Data Collection Process

- Each week OSHI received an electronic file containing all new commercial protocols submitted to CDER the previous week. The file averaged 50 protocols per week. The following protocol information was contained in the electronic file:

    - IND number
    - Serial number
    - Stamp date (indicates the date FDA received the submission)
    - Sponsor
    - Drug name
    - Indication
    - Review division

- The file was downloaded into a Microsoft Access™ database OSHI developed for the project, hereafter referred to as the OSHI database.

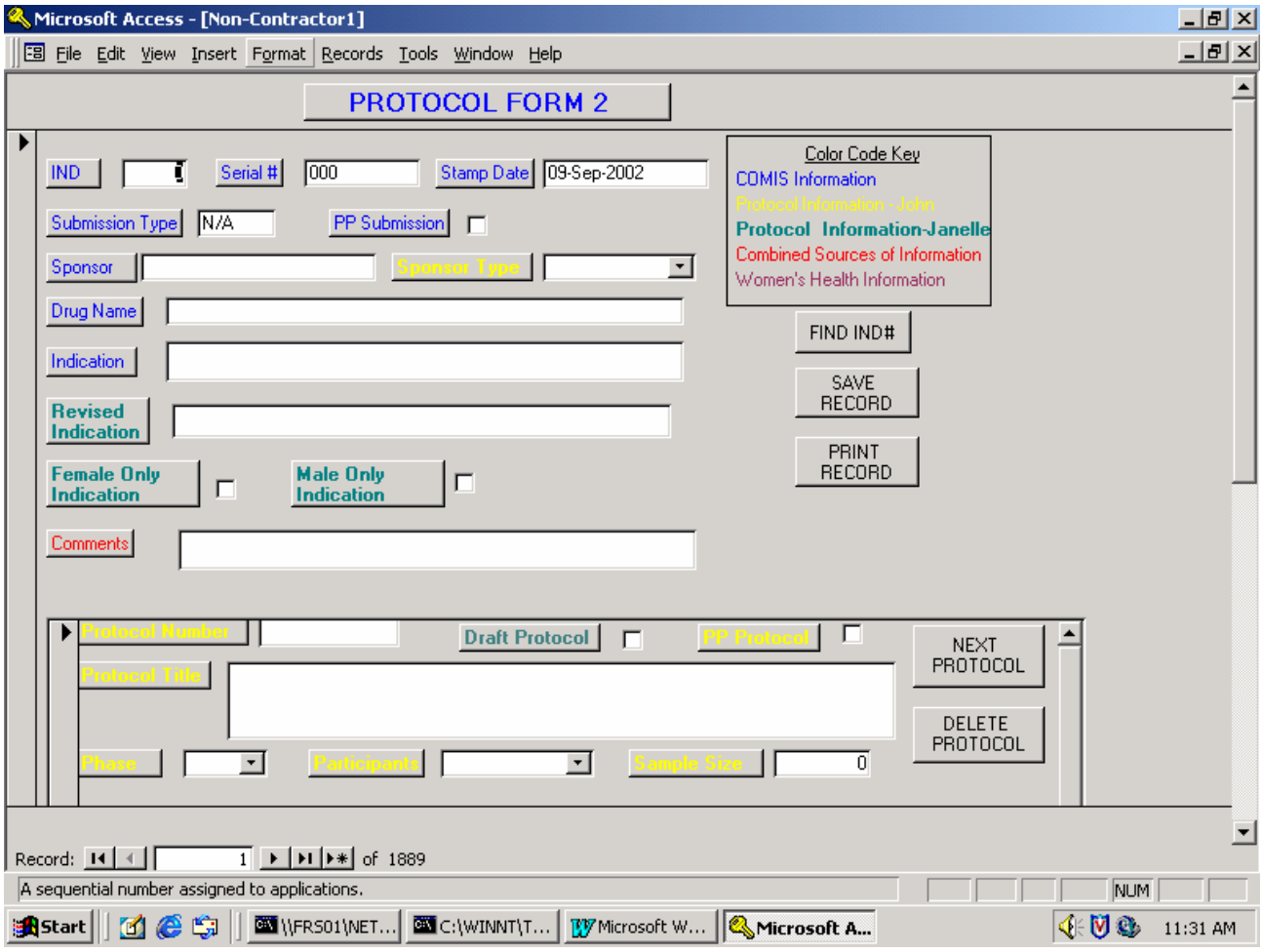
- Each week the CDER document room staff delivered copies of the paper INDs corresponding to the IND numbers and serial numbers contained in the electronic file.

- The receipt date for the paper document was entered into the database using the Document Check-In Form. (see appendix Q)

- Paper documents were placed in individual folders labeled with corresponding IND number. Documents were filed numerically by IND number.

- OSHI made two attempts to obtain all paper INDs. A total of 24 paper INDs were not received. If the paper was not received, a letter was not sent to the sponsor.

Appendix G: Protocol Form 2



Appendix H: List of Serious and Non-Serious Diseases and Conditions

The seriousness of a disease is often a matter of judgment and can vary by protocol. For purposes of this project we made a determination as to whether the disease was serious or non-serious and used this one determination for the entire project to ensure consistency. (See Chapter 7-- Limitations)

Indication	***Serious Condition****
Acne Rosacea	No
Acne Vulgaris	No
Actinic Keratosis	No
AIDS	Yes
AIDS-Associated Nephropathy	Yes
Alcoholism	Yes
Allergic Conjunctivitis	No
Allergic rhinitis	No
Alopecia	No
Alzheimer's Disease	Yes
Amyotrophic Lateral Sclerosis	Yes
Angina	No
Anxiety Disorders	No
Arrhythmias	Yes
Arteriosclerosis	Yes
Aspergillosis	Yes
Asthma	Yes
Athlete's Foot	No
Atopic Dermatitis	No
Atrial Fibrillation	Yes
Attention Deficit Hyperactivity Disorder	No
Back Pain	No
Bacterial Conjunctivitis	Yes
Bacterial Infections	No
Bacterial Infections (severe, systemic)	Yes
Bacterial Pneumonia	Yes
Bacterial Vaginosis	No
Barrett's Esophagus	Yes
Basal Cell Carcinoma	Yes

* For purposes of this project, FDA's Office of Special Health Issues classified diseases as serious or non-serious. Each CDER Division Director and the Director, Office of Medical Policy were consulted to produce the final list. This list does not have official status for any purposes other than this project.

Indication	***Serious Condition***
Bipolar Disorder	Yes
Canker Sore	No
Chronic Hepatitis B	Yes
Chronic Hepatitis C	Yes
Chronic Obstructive Pulmonary Disease	Yes
Cluster Headaches	Yes
Cocaine Addiction	Yes
Common cold	No
Congestive Heart Failure	Yes
Constipation	No
Contraception	No
Corneal Ulcer	Yes
Critical Limb Ischemia	Yes
Crohn's Disease	Yes
Cryptosporidiosis	Yes
Cystic Fibrosis	Yes
Cytomegalovirus	Yes
Deep Vein Thrombosis	Yes
Deep Vein Thrombosis (prevention)	Yes
Dementia	Yes
Dental Granuloma	No
Dermatitis	No
Diabetes Mellitus, Insulin & Non-insulin Dependent	Yes
Diabetic Foot	Yes
Diabetic Nephropathy	Yes
Diabetic Neuropathies	Yes
Diabetic Retinopathy	Yes
Diarrhea	No
Diarrhea (C. Difficile)	Yes
Dry Eye Disease	No
Dwarfism, Pituitary	Yes
Dysmenorrhea	No
Endometrial Hyperplasia	No
Endometriosis	Yes
Enuresis	No
Epilepsy	Yes
Fatty Liver	Yes
Febrile Neutropenia	Yes
Female Sexual Dysfunction	No
Fibromyalgia	No
Fragile X Syndrome/Autism	Yes

Indication	***Serious Condition***
Fungal Infections (serious systemic)	Yes
Gastroesophageal Reflux Disease	No
Gastrointestinal Hemorrhage (prevention)	Yes
Gastroparesis	No
Gaucher Disease	Yes
Genital Herpes	No
Genital Warts	No
Gingivitis	No
Glaucoma	Yes
Goiter	No
Gout	Yes
Graft vs. Host Disease	Yes
H.Pylori Eradication	No
Hepatitis B	Yes
Hepatitis C	Yes
HIV	Yes
HIV Wasting Syndrome	Yes
HIV-Associated Lipodystrophy Syndrome	Yes
Hypercholesterolemia	Yes
Hyperlipidemia	Yes
Hyperparathyroidism	Yes
Hypertension	Yes
Hypocalcemia	Yes
Hypogonadism	Yes
Hypothyroidism	Yes
Impotence (erectile dysfunction)	No
Inappropriate ADH Syndrome	Yes
Intermittent Claudication	No
Interstitial Cystitis	Yes
Intraocular Lens Implantation	Yes
Iron-Deficiency Anemia	No
Irritable Bowel Syndrome	Yes
Juvenile Rheumatoid Arthritis	Yes
Keratosis	No
Kidney Failure	Yes
Kidney Failure, Chronic	Yes
Leber Optic Atrophy	Yes
Leishmaniasis	Yes
Leprosy	Yes
Lice	No
Lupus	Yes

Indication	***Serious Condition***
Macular Degeneration	Yes
Major Depression	Yes
McCune-Albright Syndrome	No
Metabolic Syndrome X	No
Migraine	No
Mucosal Candidiasis	No
Multiple Sclerosis	Yes
Muscle Spasms	No
Muscle Spasticity	No
Myocardial Infarction	Yes
Myocardial Ischemia	Yes
Narcolepsy	Yes
Nausea & Vomitting (chemotheraphy-induced)	Yes
Neonatal Jaundice	Yes
Neurogenic Bladder Disorder	Yes
Neuropathic Pain	Yes
Neutropenic Fever	Yes
Niemann-Pick Disease (type C)	Yes
Obesity	Yes
Onychomycosis	No
Osteoarthritis	Yes
Osteogenesis Imperfecta	Yes
Osteoporosis	Yes
Otitis Externa	No
Otitis Media	No
Otitis Media with Effusion	No
Paget's Disease	Yes
Pain (acute, post-op)	No
Pain (chronic, moderate to severe)	Yes
Pain (mod to sev, chronic, or breakthrough cancer pain)	Yes
Pancreatic Insufficiency	Yes
Panic Disorder	No
Parkinson's Disease	Yes
Periodontitis	No
Polycystic Ovary Syndrome	Yes
Post-traumatic Stress Disorder	Yes
Premature Ejaculation	No
Prevention of HIV & other STDs using topical microbicides	No
Proctocolitis	Yes
Prostate Cancer	Yes
Psoriasis	Yes

Indication	***Serious Condition***
Puberty, Delayed	No
Pulmonary Hypertension	Yes
Quadriplegia	Yes
Radius Fractures (Colles' Fracture)	No
Respiratory Distress Syndrome	Yes
Respiratory Tract Infections	No
Respiratory Tract Infections (severe, bacterial)	Yes
Restless Legs Syndrome	No
Retinal Neovascularization	Yes
Rheumatoid Arthritis	Yes
Ringworm	No
Schizophrenia	Yes
Seasonal Affective Disorder	Yes
Seborrheic Dermatitis	No
Sepsis	Yes
Sexually transmitted diseases	Yes
Short Bowel Syndrome	Yes
Sickle Cell Anemia	Yes
Sinusitis	No
Sleep Apnea	Yes
Sleep Disorders	No
Smoking Cessation	No
Spinal Cord Injuries	Yes
Staphylococcal Skin Infections	No
Staphylococcal Skin Infections (severe, systemic)	Yes
Stroke	Yes
Sunburn	No
Tay-Sachs Disease	Yes
Tinea Versicolor	No
Tinnitus	No
Transplant Rejection	Yes
Ulcerative Colitis	Yes
Urinary Incontinence	Yes
Uterine Fibroids	Yes
Uveitis	Yes
Vasomotor Symptoms (hot flashes)	No
Vitamin B12 Deficiency	No
Vulvovaginal Candidiasis	No

APPENDIX I

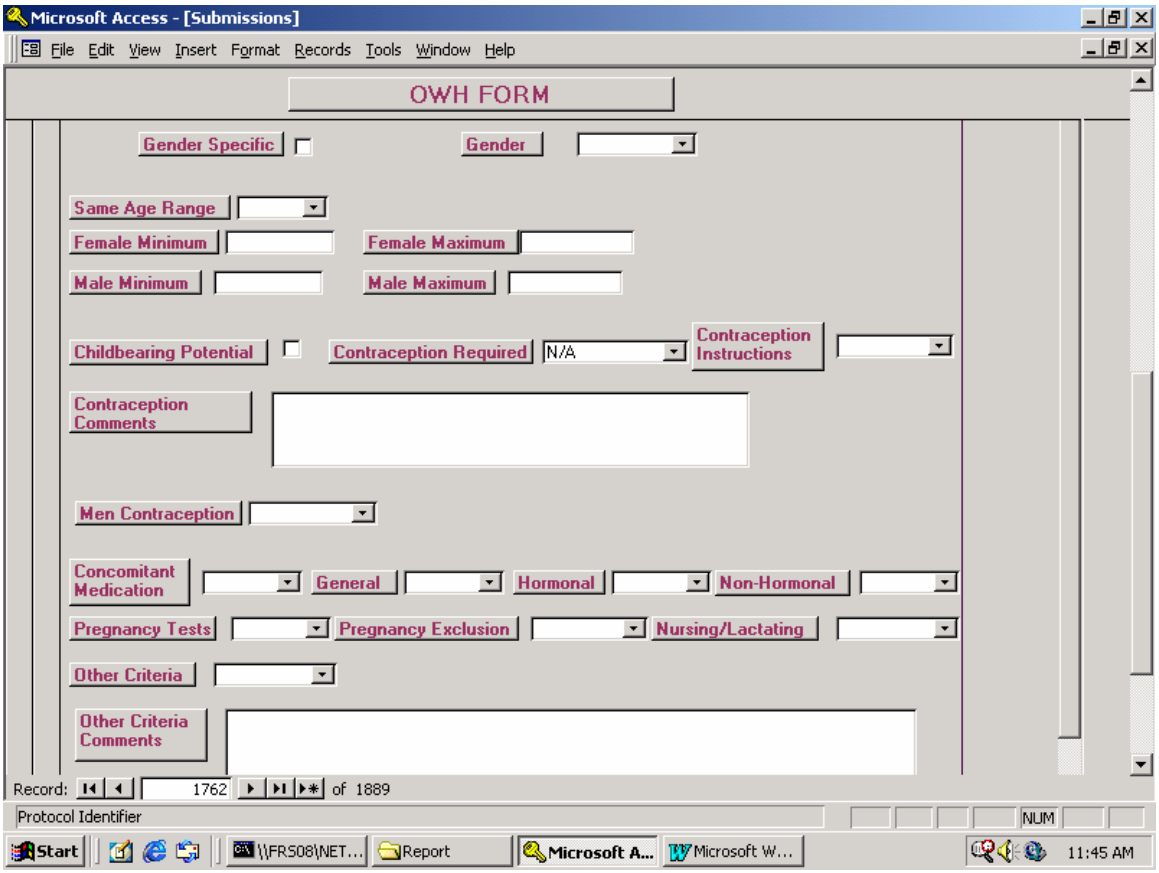
Appendix I: Compliance Evaluation Program I: Additional Data Elements

Data Elements	Description
Gender-specific indication	Female or male only indication (ex: prostate cancer, uterine cancer).
Sample Size	Number of planned participants in the trial.
Location	Domestic, international, or both. Further divided by country/region: US, Canada, Asia, Africa, South Africa, Other (Africa), Central/South America, New Zealand/Australia, Middle East, Europe, European Union, Non-European Union.
Pediatric Protocol	For purposes of this project, pediatric defined as patients < 18 years of age.
Participants	Disease status of study participant--healthy or diseased.

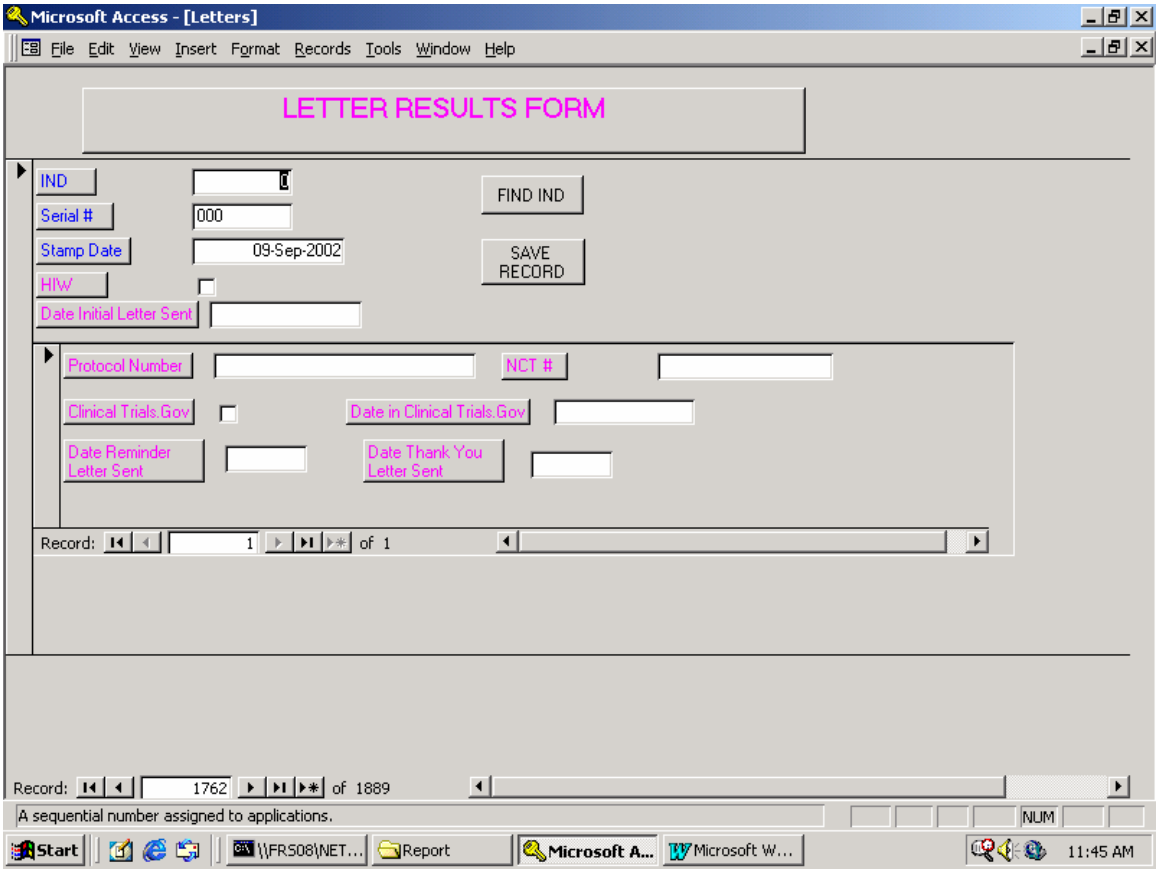
Appendix J: Data Elements Extracted for Office of Women's Health Project

OWH Data Elements	Description
Age	Eligible age range of study participants.
Women of childbearing potential	Are women of childbearing potential allowed to participate in the study?
Contraception for men	Are men required to use contraception?
Contraception for women	Are women required to use contraception?
Contraception instructions	Are there specific instructions regarding contraception?
Concomitant medication	Is concomitant medication use excluded? If yes, does the study exclude use of hormonal and/or non-hormonal medication?
Pregnancy test	Is a pregnancy test required?
Pregnant or lactating	Are women who are pregnant or nursing eligible to participate?

Appendix K: Office of Women's Health Data Entry Form



Appendix L: Letter Results Data Entry Form



Appendix M: Thank You Letter

U.S. Department of Health and Human Services
FDA Food and Drug Administration

Dear _____,

Thank you for listing information about your protocol in the *ClinicalTrials.gov* Data Bank. *ClinicalTrials.gov* provides patients, family members, health care professionals, and members of the public easy access to information on clinical trials for a wide range of diseases and conditions. *ClinicalTrials.gov* receives over 2 million page views per month and hosts approximately 7,200 visitors daily.

We appreciate your support of the Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions. If you have any questions or comments, please do not hesitate to contact Janelle Derbis, Pharm.D. or me by phone at (301) 827-4460 or email at 113trials@oc.fda.gov. Thank you for your cooperation.

Sincerely,

Theresa Toigo, R.Ph., M.B.A.
Director
Office of Special Health Issues
Office of Communications and Constituent Relations
Office of the Commissioner

Appendix N: Compliance Evaluation Program II: Data Collection Process

- OSHI received from CDER two electronic Microsoft Excel™ spreadsheets: one containing original INDs and one containing new protocols for existing INDs submitted to the Division of Oncology Drug Products (DODP). The following protocol information was contained in the electronic file:

    - IND number
    - Serial number
    - Submission date (indicates the date the sponsor filed the submission)
    - Stamp date (indicates the date FDA received the submission)
    - Sponsor name
    - Drug name (brand and generic)

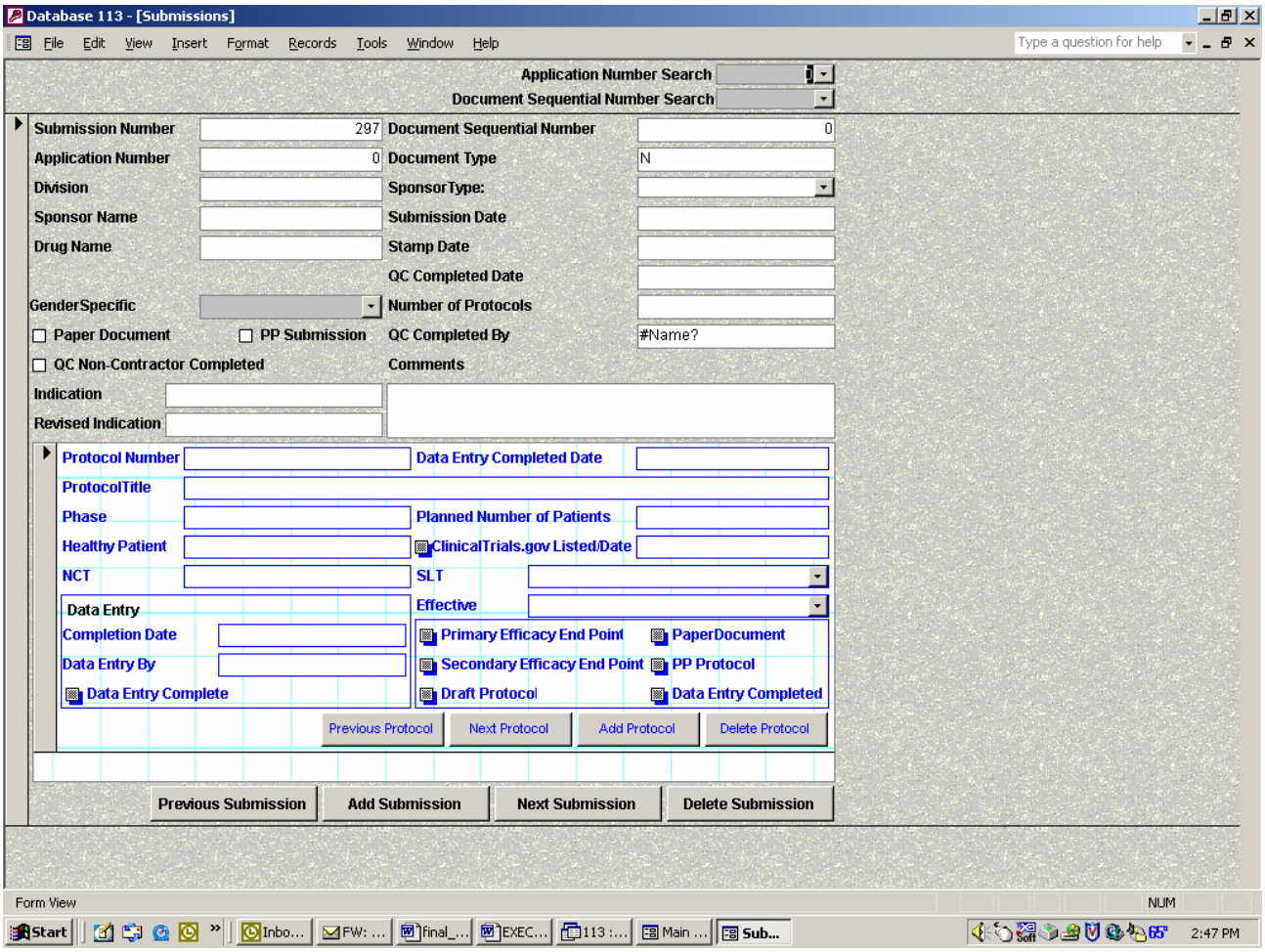
- The Excel spreadsheets were downloaded into a Microsoft Access™ database OSHI developed for Compliance Evaluation Program II.

- OSHI received copies of the paper INDs from the CDER document room staff.

- OSHI filed the paper documents in individual folders labeled with corresponding IND number. Documents were filed numerically by IND number.

APPENDIX O

Appendix O: Submissions Form



APPENDIX P

Appendix P: Trial Site Location Letter

Dear _____,

We have received inquiries from trial sponsors about the trial location and contact data element fields when submitting clinical trial information to *ClinicalTrials.gov.*

The purpose of *ClinicalTrials.gov* is to inform members of the public about potential trials for which they may be eligible. Some patients are willing to travel anywhere to participate in a study and others want to restrict their travel. The latter group limits their searches to locations to which they are willing to travel. For example, a patient who has relapsed with metastatic lung cancer may be unable to travel more than ten or fifteen miles from their home. On the other hand, a newly diagnosed relatively healthy stage three kidney cancer patient may be willing to travel anywhere to be in a clinical trial. Please include the city, state, and country for each clinical trial site so that visitors to *ClinicalTrials.gov* may search for clinical trials by location. We also ask that you consider including the name of the facility conducting the trial.

We require contact information in the form of a phone number or email address so visitors to the site can call or e-mail to obtain additional information about the trial. The contact can be a central contact such as Clinical Trial Coordinating Center,1-800-123-1234 or a specific contact such as Dr. Mary Jones, mjones@institution.org for each site.

The protocol records (NCT 00000001, NCT 00000002, NCT 00000003) do not provide visitors to *ClinicalTrials.gov* with sufficient location and/or contact information.

Because you are currently omitting the location and/or contact information when you enter your protocol into the Protocol Registration System (PRS), patients will not find your trial as a potential option when searching by location. We ask that you make the necessary changes through the PRS at https://register.clinicaltrials.gov/ and re-release the record.

If you have any questions, please call me at (301) 827-4460. Thank you in advance for your understanding and support.

Sincerely,
Theresa Toigo, RPh, MBA
Director, Office of Special Health Issues
Office of External Relations
Food and Drug Administration

Appendix Q: Document Check-In Data Entry Form